Rationale and Design of LAPIS: A Multicenter Prospective Cohort Study to Investigate the Efficacy and Safety of Low-Dose Aspirin in Elderly Chinese Patients

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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 (CVDs) and hemorrhage. While the adverse effects of aspirin can be reduced by using the lowest effective dose, its optimal dose remains undetermined in the elderly Chinese population with both higher cardiovascular and bleeding risks. This study aims to assess the current status of aspirin therapy in real-world clinical settings as well as investigate the efficacy and safety of different doses of aspirin intake (≤ 50 mg/d and > 50 mg/d) for CVD prevention and management in elderly Chinese individuals.

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. At least 10,000 people aged ≥ 60 years who require long-term aspirin therapy will be recruited. The effectiveness outcome is a composite of major cardiovascular events (MACEs), including nonfatal myocardial infarction, unstable angina, arteriosclerotic disease requiring surgery or intervention, nonfatal stroke, transient ischemic attack, or cardiovascular death (excluding intracranial hemorrhage). The safety outcome is a composite of the first occurrence of fatal bleeding, major bleeding and minor bleeding. Information on the incidence of aspirin-associated gastrointestinal adverse events will also be collected for safety analyses. Outcome measurements will be performed at intervals of 30 days, 3 months, 6 months and then every 6 months for the next 3 years.

Conclusion: The results of the LAPIS study will ascertain the efficacy and safety of different doses of aspirin for the prevention and management of CVD, thereby providing evidence to determine the optimal evidence-based dose of aspirin therapy in Chinese elderly individuals.

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

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

Introduction

Cardiovascular disease (CVD) is the leading cause of disability and death in the elderly population. This condition has become a growing public health concern in China, with CVD prevention as a top priority. Although aspirin reduces the occurrence of atherothrombosis,1,2 and is considered an established agent for the chemoprevention of colorectal cancer (CRC),3–5 this medication is associated with a high risk of bleeding.6 Low-dose aspirin has been shown to be effective in the secondary prevention of CVD, with cardiovascular benefits outweighing the risk of hemorrhage.1,7 However, the role of aspirin in primary prevention trials of patients whose CVD risk is lower than that in secondary prevention trials remains debatable. Moreover, the US Preventive Services Task Force (USPSTF)8 recommends against initiating aspirin at 75–100 mg/d for the primary prevention of CVD in adults aged ≥ 60 years. Since the risk of atherothrombosis is higher in the elderly population, the potential benefits of aspirin may be greater in these subjects than
in younger adults. Therefore, the limited use of aspirin may indiscriminately reduce its net benefit, particularly in patients with a high 10-year risk of myocardial infarction or stroke. Moreover, an increased risk of bleeding has been observed in elderly individuals, particularly in elderly Chinese individuals with lower body weights and Helicobacter pylori infection, which leads to the discontinuation of aspirin therapy. Therefore, before prescribing aspirin, the balance between cardiovascular benefits and potential risk of hemorrhage should be considered.

Aspirin dose is reportedly associated with a risk of bleeding. Currently, the recommended dose of aspirin for the primary and secondary prevention of CVD is 75–100 mg/d based on clinical guidelines, aspirin 50 mg/d is only recommended for preventing stroke and other cardiovascular events for patients with noncardiogenic transient ischemic attacks (TIA) or ischemic stroke, and evidence of lower doses of aspirin for the primary and secondary prevention of CVD is lacking. Nevertheless, owing to the risk of bleeding in elderly individuals, physicians in real-world clinical practice prescribe a lower dose of aspirin than the recommended dose. Some studies conducted by our team focused on the difference in outcomes between the recommended aspirin doses and lower doses (≤ 50 mg/d) in elderly Chinese individuals. An observational, retrospective study showed that aspirin at a dose of 40 mg/d could significantly inhibit platelet aggregation and reduce the risk of bleeding and other adverse reactions in patients with very advanced ages. A multicenter, randomized controlled trial showed that aspirin at 50 mg/d and 100 mg/d in elderly individuals had similar antiplatelet aggregation effects and good short-term safety profiles. Moreover, a single-center interim analysis of a multicenter, prospective, observational cohort study indicated that 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. However, evidence from the elderly Chinese population is still lacking, and the effective and safe dose of aspirin in the elderly remains unknown.

In these contexts, we will carry out this multicenter, prospective, observational cohort study to assess the current situation of aspirin therapy in real-world clinical settings as well as investigate the efficacy and safety of different doses of aspirin intake (≤ 50 mg/d and > 50 mg/d) for CVD prevention and management in Chinese individuals over 60 years of age.

Materials and Methods
Study Objectives and Hypothesis
The main objective of this study was to assess the current situation of aspirin therapy in real-world clinical settings and to investigate the efficacy and safety of different doses of aspirin intake (≤ 50 mg/d and > 50 mg/d) for CVD prevention and management in elderly Chinese individuals. We hypothesize that a lower dose of aspirin (≤ 50 mg/d) in Chinese individuals over 60 years of age will lead to similar cardiovascular benefits but fewer bleeding events than the recommended dose of aspirin (> 50 mg/d).

Study Design
Low-dose aspirin for primary and secondary prevention of CVD in the elderly study (LAPIS; chictr.org.cn, ChiCTR1900021980) is a multicenter, prospective, observational cohort study. Participants are being recruited from 50 to 100 centers across China. Enrollment began in April 2019, and the study will be completed in 2024. The LAPIS procedures do not interfere with aspirin therapy given to the patients, and the dosage and treatment duration of aspirin are decided by the treating physician. The combined use of antiplatelet drugs (such as clopidogrel, ticagrelor, and cilostazol) or anticoagulant drugs (such as warfarin, dabigatran, rivaroxaban, and edoxaban) will not be altered at the discretion of the clinicians and documented in the case report form (CRF). The observation period was defined as the time between enrollment and the final visit for general examination (at least 3 years for each participant). Participants will be followed up on the 30th day, 3rd and 6th months, and then every 6 months (at least 9 times) until the end of the LAPIS study. Outpatient/inpatient face-to-face or phone/WeChat visits will be used for follow-up visits. At each visit, an independent group of physicians will carefully examine and verify all events. Information about the continuation or temporary interruption of aspirin, laboratory tests, concomitant medications, and detailed information about major cardiovascular events (MACEs), bleeding, and gastrointestinal events will be recorded. If a patient withdraws or is lost to follow-up, observation will be terminated, and the date and reason will be recorded. A flow chart of the study is shown in Figure 1. The study visit schedules and assessments are shown in Table 1.
Chinese patients ≥ 60 years old taking aspirin for primary and secondary prevention of cardiovascular disease

Criteria for inclusion and exclusion

Baseline data

The treating physicians determined the dosage and duration of aspirin

aspirin >50 mg/d

aspirin ≤50 mg/d

Follow-up at least 3 years

Efficacy and safety of aspirin > 50 mg/d and aspirin ≤50 mg/d

Dose of aspirin
Demographic information
Clinical information
Comorbidities
Concomitant Prescription information
Laboratory tests

Dose of aspirin
Comorbidities
Concomitant Prescription information
Laboratory Tests
Major cardiovascular events
Bleeding events
Gastrointestinal events

Figure 1 Flow chart of the LAPIS study.

Table 1 Schedule of Enrollment, Follow-Up, and Assessments for LAPIS

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Note: ×, needed.
Study Population
Participants aged ≥ 60 years who require long-term aspirin for the primary and secondary prevention of CVD and can provide routine laboratory test results for the past 3 months will be recruited. Participants will be excluded from the study if they meet any of the following conditions: (1) allergy to aspirin, salicylate, or any other ingredients of aspirin; (2) a history of asthma caused by salicylate, salicylate substances, or nonsteroidal anti-inflammatory drugs; (3) life expectancy ≤ 3 years; and (4) refusal to provide written informed consent or difficulty with medication or regular follow-up.

Baseline Data Collection
The baseline data of all participants will be collected after obtaining their informed consent at the initial visit. Demographic information will include age, sex, body weight, smoking history, and alcohol intake. Clinical information will include vital signs, previous history of MACEs (nonfatal myocardial infarction, unstable angina, vascular diseases requiring surgical/interventional revascularization, nonfatal stroke, or transient ischemic attack), hemorrhagic events, gastrointestinal disease, and comorbidities (hypertension, diabetes mellitus, dyslipidemia, or chronic kidney disease). Laboratory tests performed 3 months prior to enrollment included routine blood examination (leukocyte count, hemoglobin, hematocrit, and platelet count), liver function (alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, total bile acid, alkaline phosphatase, gamma-glutamyl transeptidase), renal function (serum urea nitrogen, uric acid, serum creatinine, and estimated glomerular filtration rate), serum glucose (fasting blood glucose and glycosylated hemoglobin), serum lipids (triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol), and coagulation function evaluation. Prescription information will include the status of aspirin intake and concomitant antithrombotic therapy and other concomitant medications, such as β-blockers, statins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), proton pump inhibitors (PPIs), and histamine 2 receptor antagonists (H2RAs). Baseline information will be recorded in detail in the CRF.

Study Outcomes
Effectiveness Outcomes
The primary effectiveness outcome is a composite of the first occurrence of MACEs, including nonfatal myocardial infarction, unstable angina, arteriosclerotic disease requiring surgery or intervention, nonfatal stroke, transient ischemic attack, and cardiovascular death (excluding intracranial hemorrhage). The most important secondary effectiveness outcomes are as follows: (1) composite of the first nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death (excluding intracranial hemorrhage); (2) first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death (excluding intracranial hemorrhage); (3) first occurrence of unstable angina; (4) first occurrence of arteriosclerotic disease requiring surgery or intervention; (5) first occurrence of transient ischemic attack; and (6) all-cause mortality.

Safety Outcomes
The safety outcome is a composite of the first occurrence of fatal bleeding (Bleeding Academic Research Consortium,17 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, including new-onset gastroduodenal ulcer, reflux esophagitis, erosive gastritis, stomach or abdominal discomfort, pain, pressure, heartburn, and nausea, will be collected.

Sample Size Calculation
The recommended dose of aspirin for the primary and secondary prevention of CVD is 75–100 mg/d. Although previous studies have shown that short-term use of aspirin at 40–50 mg/d inhibits platelet aggregation,14,15 there is no evidence of long-term use of aspirin ≤ 50 mg/d in elderly Chinese individuals. According to the single-center interim analysis of the Peking University First Hospital from April 2019 to February 2022,16 165 patients receiving aspirin at 50 mg/d and 261 patients receiving aspirin at 100 mg/d were enrolled in the study. After adjusting for patient characteristics using propensity score matching (PSM), the bleeding event rate was 22.81% in the 50 mg/d aspirin group and 34.21% in the 100 mg/d aspirin group, with a median follow-up period of 691 days. A sample size of 570 patients (190 patients in the 50 mg/d aspirin group and 380 patients in the 100 mg/d group) will be sufficient to provide 80% power at a 0.05 two-sided α level of significance for safety.
assessments. However, since the MACE rates were similar between the 50 mg/d aspirin group (9.65%) and the 100 mg/d aspirin group (9.65%), it is difficult to calculate the sample size with a particular statistical method for efficacy assessment. Given the exploratory nature of this study, a sample size of > 10,000 is considered efficient to determine the safety and efficacy of each dose of aspirin in elderly individuals. The LAPIS research team will analyze the data annually and adjust the sample size accordingly.

**Statistical Analysis**
Data will be presented as the mean ± standard deviation (SD) or median (interquartile range) for continuous variables and percentage (%) for categorical variables. Normally distributed continuous variables will be compared using independent sample t-tests. A paired t-test or Wilcoxon rank-sum test will be used to compare continuous variables between the two groups, while ANOVA or the Kruskal–Wallis rank-sum test will be used for multigroup comparisons. All categorical variables will be compared using Pearson’s χ² test or Fisher’s exact test. Subgroup analysis will be performed based on primary prevention and secondary prevention. Patient characteristics will be compared between patients who received > 50 mg/day aspirin and those who received ≤ 50 mg/day aspirin. PSM with a 1:1 ratio will be performed to adjust for patient characteristics and directly compare outcomes between the two groups. The standardized difference will be calculated to compare patient characteristics between the two groups. Kaplan-Meier analysis with Cox proportional hazards regression will be used for time-to-event analysis to determine hazard ratios (HRs) and 95% confidence intervals (CIs). The Log rank test will be conducted for the overall survival curves. Multivariate Cox proportional hazards models will be developed to identify the independent predictors of MACEs and bleeding events after adjusting for the variables that were known to be strongly associated with the risk of MACEs and bleeding events or differed significantly by univariate analysis. All tests will be two-sided with a significance level of 0.05, unless stated otherwise. Statistical analyses will be performed using SPSS Statistics (version 23.0; IBM, Armonk, NY, USA).

**Data Management**
The data manager will establish an electronic data capture (EDC) system based on eCRF (www.91trial.com). An investigator will enter data from electronic medical records into the EDC system at each site. Supervisors will review the information in the EDC system weekly and conduct a visit every 6 months. The data manager is responsible for designing and managing the EDC system database. At the end of the LAPIS study, the data manager will locate the database.

**Ethical Approval and Study Registration**
The LAPIS study was approved by the Institutional Ethics Committee of the Peking University First Hospital (approval number 2018[248])) and will be conducted in accordance with the Declaration of Helsinki. Before patient enrollment, the protocol and consent forms were approved by the institutional review board of each participating center. All participants will provide written informed consent before enrollment in the study.

The study protocol was registered in the Chinese Clinical Trials Registry on March 19, 2019 with the identification code ChiCTR1900021980.

**Discussion**
CVD is a serious threat to elderly individuals. Approximately 330 million people suffer from CVD in China, accounting for 43.81% of deaths among urban residents and 46.66% among rural residents. Platelet activation and aggregation are the primary causes of arterial thrombosis. Aspirin, a platelet aggregation inhibitor, has been shown to play an important role in the primary and secondary prevention of CVD. In addition, aspirin is considered the most established agent for chemoprevention of CRC with the delayed impact due to remarkably consistent data from previous cohort studies and randomized clinical trials, it is reported that the effects of aspirin on cancer are not apparent until at least 3 years after the start of use, and some benefits are sustained for several years after cessation in long-term users. A pooled analysis also indicated that regular use of aspirin was associated with a lower risk of CRC for individuals who used aspirin before age 70 years and continued into their 70s or later compared with non regular users.
However, this medication is associated with an increased risk of hemorrhagic events. Aspirin decreases gastric mucosal prostaglandin levels and causes significant gastrointestinal mucosal damage, acid back diffusion and impaired platelet aggregation, further inducing direct epithelial damage.24 It has been reported that gastrointestinal adverse reactions are significantly more common than clinically overt bleeding in individuals on antiplatelet therapy.25-27 Helicobacter pylori infection is a recognized risk factor for gastrointestinal bleeding during low-dose aspirin treatment, and the infection should be eradicated when identified, especially for Chinese individuals due to the higher prevalence.28 Furthermore, the risk of bleeding increases when aspirin is combined with other antiplatelets and anticoagulants.29,30 The benefit of low-dose aspirin at 75–100 mg/day in the secondary prevention of CVD is well established, while the role of low-dose aspirin in primary prevention is still being debated. The JPPP,31 ARRIVE,32 ASCEND,33 and ASPREE34 clinical trials, as well as a previous meta-analysis,35 have shown inconsistent cardiovascular outcomes with potential benefits offset by increased bleeding risk, and the ASPREE trial found aspirin use to be associated with an increased risk of CRC mortality in older adults at 4.7 years of follow-up.34 Older adults are at a higher risk for both atherosclerotic thrombosis and bleeding, and the bleeding risk associated with aspirin has been shown to increase with age and aspirin dose.22 Some post hoc analyses of randomized controlled trials and observational studies have indicated that the adverse effects of aspirin therapy can be minimized by administering a lower dose,36 which also improves long-term adherence.37

Previous studies have explored the relationship between body weight and the antiplatelet effects of aspirin.38,39 These results suggest an association between body weight and aspirin dosage: low-dose aspirin (75–100 mg/d) is only effective in preventing vascular events in patients weighing less than 70 kg,40 and patients weighing < 60 kg are more likely to experience bleeding events.41,42 In addition, aspirin-mediated reductions in the long-term risk of CRC are also weight dependent, and it has been reported that aspirin 75–100 mg/d reduces the risk of CRC in participants weighing less than 70 kg but not in people weighing 70 kg or more.40 Therefore, a one-dose-for-all approach to aspirin use in elderly individuals is unlikely to be optimal and an individualized therapeutic strategy is warranted. In clinical practice, most physicians are reluctant to prescribe standard-dose aspirin to elderly patients because of the increased risk of bleeding, particularly in patients who are taking other antithrombotic medications. Few studies have focused on the difference in outcomes between the recommended aspirin doses and lower doses(≤ 50 mg/d) in elderly Chinese individuals, and the effective and safe dose of aspirin in elderly individuals remains unknown. Therefore, additional data from large-scale clinical studies should be collected and analyzed in elderly populations with higher comorbidities, polypharmacy, lower body weight, and frailty.

To the best of our knowledge, the LAPIS study will be the first large-scale multicenter prospective observational cohort study to evaluate the efficacy and safety of different doses of aspirin for the primary and secondary prevention of CVD in elderly Chinese individuals. At least 10,000 participants ≥ 60 years of age will be enrolled in the study to provide important information about aspirin treatment in the Chinese elderly population in a real-world clinical setting. We will compare the cardiovascular benefits, bleeding, and gastrointestinal adverse effects of aspirin ≤ 50 mg/d vs aspirin > 50 mg/d in elderly Chinese individuals, particularly in those with a high risk of bleeding or concomitant antithrombotic therapy.

The LAPIS study will help determine the optimal dose of aspirin for elderly Chinese individuals. The first participant was enrolled in the LAPIS study on April 1st, 2019. As of the date of manuscript submission, 6769 patients have been enrolled from 77 medical centers in 11 Chinese provinces. The study is expected to continue for 5 years, with the final participant visit scheduled for 2024. We look forward to the LAPIS study, which will provide useful information for the overall management of CVD in older adults.

Conclusions
Low-dose aspirin for primary and secondary prevention of CVD in the elderly study (LAPIS) is a multicenter, prospective, observational cohort study that aims to assess the current status of aspirin therapy in real-world clinical settings as well as investigate the efficacy and safety of different doses of aspirin intake (≤ 50 mg/d and > 50 mg/d) for CVD prevention and management in elderly Chinese individuals. It is expected that the results of this study will provide evidence to determine the optimal evidence-based dose of aspirin therapy in Chinese elderly individuals.
Data Sharing Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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.

References


