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Effect of Aspirin on Disability-free Survival in the Healthy Elderly

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ABSTRACT

BACKGROUND

Information on the use of aspirin to increase healthy independent life span in older persons is limited. Whether 5 years of daily low-dose aspirin therapy would extend disability-free life in healthy seniors is unclear.

METHODS

From 2010 through 2014, we enrolled community-dwelling persons in Australia and the United States who were 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States) and did not have cardiovascular disease, dementia, or physical disability. Participants were randomly assigned to receive 100 mg per day of enteric-coated aspirin or placebo orally. The primary end point was a composite of death, dementia, or persistent physical disability. Secondary end points reported in this article included the individual components of the primary end point and major hemorrhage.

RESULTS

A total of 19,114 persons with a median age of 74 years were enrolled, of whom 9525 were randomly assigned to receive aspirin and 9589 to receive placebo. A total of 56.4% of the participants were women, 8.7% were nonwhite, and 11.0% reported previous regular aspirin use. The trial was terminated at a median of 4.7 years of follow-up after a determination was made that there would be no benefit with continued aspirin use with regard to the primary end point. The rate of the composite of death, dementia, or persistent physical disability was 21.5 events per 1000 person-years in the aspirin group and 21.2 per 1000 person-years in the placebo group (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11; P=0.79). The rate of adherence to the assigned intervention was 62.1% in the aspirin group and 64.1% in the placebo group in the final year of trial participation. Differences between the aspirin group and the placebo group were not substantial with regard to the secondary individual end points of death from any cause (12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group), dementia, or persistent physical disability. The rate of major hemorrhage was higher in the aspirin group than in the placebo group (3.8% vs. 2.8%; hazard ratio, 1.38; 95% CI, 1.18 to 1.62; P<0.001).

CONCLUSIONS

Aspirin use in healthy elderly persons did not prolong disability-free survival over a period of 5 years but led to a higher rate of major hemorrhage than placebo. (Funded by the National Institute on Aging and others; ASPREE ClinicalTrials.gov number, NCT01038583.)

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*A complete list of the ASPREE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Several large, randomized trials have shown the efficacy of aspirin for the secondary prevention of cardiovascular disease among persons with a history of coronary heart disease or stroke.[1-3] The evidence supporting a benefit of aspirin therapy in the primary prevention of cardiovascular or other chronic disease is less conclusive despite favorable trends suggesting that aspirin use reduces the incidence of cardiovascular events and possibly reduces the incidence of cancer and cancer-related mortality, particularly from colorectal cancer.[4-8] Among elderly persons (more so than among younger persons), a higher risk of cardiovascular disease may increase the benefit of aspirin, but this benefit may be accompanied by an increased risk of bleeding.[7,9,10] Despite the widespread use of low-dose aspirin in elderly persons who do not have a medical indication for aspirin, there is limited evidence that the beneficial effects outweigh the risks in this age group.

We conducted the Aspirin in Reducing Events in the Elderly (ASPREE) trial, which was a randomized, placebo-controlled trial to investigate whether the daily use of aspirin, at a dose of 100 mg, in healthy, community-dwelling older adults would prolong healthy life span, free from dementia and persistent physical disability. We measured the primary end-point events of death, dementia, and persistent physical disability, from which we derived the composite primary end point of disability-free survival, which was used to reflect a healthy life span. This end point was chosen to allow an integrated assessment of the overall risk–benefit ratio associated with the use of aspirin in this population.

METHODS

TRIAL DESIGN

We conducted this randomized, double-blind, placebo-controlled trial at 34 sites in the United States and at 16 sites in Australia. The trial evaluated the effect of 100 mg of enteric-coated aspirin daily, as compared with matching placebo. Details of the trial design and rationale have been published previously.[11,12] Bayer Pharma (Germany) provided the trial drug (aspirin) and placebo but had no other role in the trial. The Department of Epidemiology and Preventive Medicine at Monash University in Australia coordinated the data collection and was responsible for statistical analyses. Coordination of the trial and monitoring of sites was conducted by this department in Australia and by the Berman Center for Outcomes and Clinical Research in the United States.

The trial was conducted according to the criteria of the International Conference on Harmonisation for the conduct of clinical trials. The institutional review board at each participating institution approved the trial, and all the participants provided written informed consent. The authors designed the trial and gathered and analyzed the data. The first and second authors wrote the first draft of the manuscript. All the authors vouch for the validity of the trial results, the adherence of the trial to the protocol (available with the full text of this article at NEJM.org), and the completeness and accuracy of the reporting of adverse events. There was no commercial support for this trial.

TRIAL POPULATION

Trial participants were community-dwelling men and women from Australia and the United States who were 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States). Details of the recruitment methods have been published previously.[11] In Australia, general practitioners and trial personnel identified potentially eligible patients, who were then sent a letter of invitation to participate. In the United States, potential participants were identified by means of clinic-based mailing lists and screening of electronic medical records or by responses to media advertisements and were subsequently invited to participate by letter.

The eligibility criteria are listed in Table S1 in the Supplementary Appendix (available at NEJM.org) and have been reported previously.[11,13] Persons 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States) were required to be free from any chronic illness that would be likely to limit survival to less than 5 years and to be free from documented cardiovascular or cerebrovascular disease. The rationale for the younger age selection of blacks and Hispanics was based on their higher risk of cardiovascular disease or dementia.[11,14,15]

Key exclusion criteria were a clinical diagnosis of dementia, a known high risk of bleeding, or a contraindication to aspirin (see the Supplementary Appendix). Potential participants were also excluded if they had a score of less than 78 on the Modified Mini–Mental State Examination (on a scale from 0 to 100, with higher scores

indicating better function)[16] or had substantial physical disability, defined as a score of 4 or 5 for any one of the six basic activities of daily living (bathing, dressing, toileting, transferring, walking, and feeding) on the Katz Index of Independence in Activities of Daily Living (scores for each activity range from 1 [no difficulty] to 5 [unable to do]; a score of 4 indicates severe difficulty in performing the activity).[17]

TRIAL PROCEDURES

Participants who met the eligibility criteria at a screening visit were enrolled in a 4-week placebo run-in phase. Participants who had a rate of adherence to pill ingestion, as measured by pill count, of 80% or greater during the run-in phase were then randomly assigned, in a 1:1 ratio, to receive a 100-mg tablet of enteric-coated aspirin or matching placebo daily, according to a block-randomization procedure with stratification according to trial center (in the United States) or general practice clinic (in Australia) and age (65 to 79 years or ≥80 years).

Annual in-person visits were supplemented by telephone calls every 3 months to encourage retention in the trial and telephone calls every 6 months to collect additional information; details of the data-collection schedules are provided in Table S2 in the Supplementary Appendix and have been described previously.[13] Participants were considered to be lost to follow-up if, in the 12 months before June 12, 2017, trial staff had had no personal contact with them, either in person or by telephone, and if there was no record of attendance of the participant at the medical practice.

Event-adjudication committees whose members were unaware of the trial-group assignments reviewed all the primary and secondary end-point events and deaths according to established definitions (see the Supplementary Appendix). Reports on the accumulating data were reviewed at regular intervals by the trial sponsor (the National Institute on Aging) and by an independent data and safety monitoring board, whose members had been appointed by the National Institute on Aging. An international data-management committee reviewed site-monitoring reports, which included information about adherence to the protocol and data quality. The trial participants, study staff, investigators, and general practitioner associate investigators were unaware of the trial-group assignments until the publication of this article.

Adherence to the trial intervention was assessed by means of annual tablet counts on returned bottles of aspirin or placebo. The correct identity of the tablets (i.e., determination of the contents) in the labeled bottles from each batch of aspirin or placebo was confirmed by laboratory analysis (see the Supplementary Appendix). After a nonfatal end-point event, participants remained in the trial while taking their assigned trial intervention (aspirin or placebo), if they were willing.

TRIAL END POINTS

The primary end point was disability-free survival, which was defined as survival free from dementia or persistent physical disability. The primary composite end point was derived from the first occurrences of the end-point events of death, dementia, and persistent physical disability. The diagnosis of dementia was adjudicated according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition,[18] and persistent physical disability was considered to have occurred when a participant reported having an inability to perform or severe difficulty in performing at least one of the six basic activities of daily living that had persisted for at least 6 months.[17] Details regarding the health measures and definitions used in this trial are listed in Table S2 in the Supplementary Appendix.

The ASPREE trial program had eight prespecified secondary end points, including the three individual components of the primary end point — death from any cause, dementia, and persistent physical disability — as reported in this article. Other secondary end points included fatal and nonfatal cardiovascular disease (including stroke), fatal and nonfatal cancer, mild cognitive impairment, depression, and major hemorrhage (including clinically significant bleeding and hemorrhagic stroke). Further analyses of the secondary end points of death, cardiovascular disease (including stroke), and major hemorrhage are now reported in two accompanying articles in the *Journal*.[19,20]

STATISTICAL ANALYSIS

Details of the statistical analysis procedures and sample-size calculation are provided in the Supplementary Appendix. In brief, we estimated the probability of remaining event-free using the Kaplan–Meier method, and its complement, cumulative incidence, was used for plots. In intention-to-

treat analyses, Cox proportional-hazards models were used to compare the aspirin group with the placebo group with regard to time-to-event end points and to evaluate effects in subgroups with the use of interaction terms.

Subgroups that were specified in the statistical analysis plan included sex, age (younger than the median age vs. the median age or older), country of residence (Australia vs. the United States), race or ethnic group (white in Australia, white in the United States, black, Hispanic, or other), body-mass index (the weight in kilograms divided by the square of the height in meters; <20.0 [underweight], 20.0 to 24.9 [normal weight], 25.0 to 29.9 [overweight], or ≥30.0 [obese]), previous regular use of aspirin (yes vs. no), frailty category (not frail, prefrail, or frail), personal history of cancer (yes vs. no), smoking (never smoked, former smoker, or current smoker), and the presence of diabetes, hypertension, and dyslipidemia at baseline (yes vs. no, for each condition).[11,21] The frailty category was determined on the basis of the adapted Fried frailty criteria,[21] which include body weight, strength, exhaustion, walking speed, and physical activity (see the Supplementary Appendix); the category of prefrail included participants who met one or two criteria, and the category of frail included those who met three or more criteria.

There was no plan for the imputation of missing data. Data censoring occurred at the latest time point that an end point could have been reached and was assumed to be for reasons that would not alter the prospect of the participant having an end point, as compared with participants who continued to be followed. There was no plan for adjustment for multiple comparisons of secondary end points, and only point estimates with confidence intervals that were unadjusted for multiple comparisons are reported, without P values, except for the safety end point of major hemorrhage. For safety analyses, a significance level of 0.05 was applied. An interim analysis was planned for when 1893 primary end-point events had occurred, according to a Haybittle–Peto stopping rule.

RESULTS

PARTICIPANTS

Recruitment began in March 2010 and ended in December 2014, at which time 19,114 participants had undergone randomization (9525 participants to the aspirin group and 9589 to the placebo group) (Fig. 1). The demographic and clinical characteristics of the participants at baseline were similar in the two groups (Table 1, and Table S3 in the Supplementary Appendix). The median age of the participants was 74 years, and 56.4% of the participants were women.[13] A total of 8.7% of the participants were nonwhite; of these, 54.1% were black, 29.3% Hispanic, 9.9% Asian, and 6.7% of another race or ethnic group.[13] A total of 11.0% of the participants (7.2% of the participants in Australia and 36.7% of those in the United States) reported that they had been regular daily users of aspirin before participation in the trial.

Starting in February 2015, hazard ratios with 95% confidence intervals and conditional power calculations for the primary end point, without P values, were presented every 6 months at closed sessions of the data and safety monitoring board. In March 2017, the prespecified number of events that were required for the interim analysis had not been reached, but data to that time showed similar rates of the primary end point in the two trial groups. This finding made it very unlikely that continuation of the trial until its scheduled end date of December 31, 2017, would reveal a significant treatment effect with aspirin for the primary end point. In June 2017, all the trial participants were notified of the decision by the National Institute on Aging to stop the trial, and they were instructed to cease taking the trial interventions (aspirin or placebo) and to return any remaining tablets. Participants who had been scheduled for trial visits in the remainder of 2017 were requested to complete a close-out questionnaire to ensure the ascertainment of clinical events that had occurred before June 12, 2017. Persistent physical disability (of 6 months' duration) and dementia end points before this date were confirmed by follow-up until December 2017, in accordance with the protocol.

The median duration of follow-up from randomization was 4.7 years (interquartile range, 3.6 to 5.7) in each group. More than 90% of the due trial visits were completed each year (Table S4 in the Supplementary Appendix). By the last 12 months of the trial, 82.0% of participants were still attending annual follow-up visits, 5.5% had died, 9.7% were being followed up by regular telephone contact or through access to clinical and other records, 1.2% had withdrawn, and

1.6% were lost to follow-up (all the participants contributed data to the analyses until the time of withdrawal or loss to follow-up) (Table S5 in the Supplementary Appendix). Vital status of all the participants was assessed after trial closure by means of a search of national death records. In the final 12 months of the trial, 62.1% of the participants in the aspirin group and 64.1% of those in the placebo group reported that they were still taking their assigned intervention (Table S6 in the Supplementary Appendix). Details regarding adherence to the assigned regimen and the use of open-label aspirin are provided in Table S7 in the Supplementary Appendix.

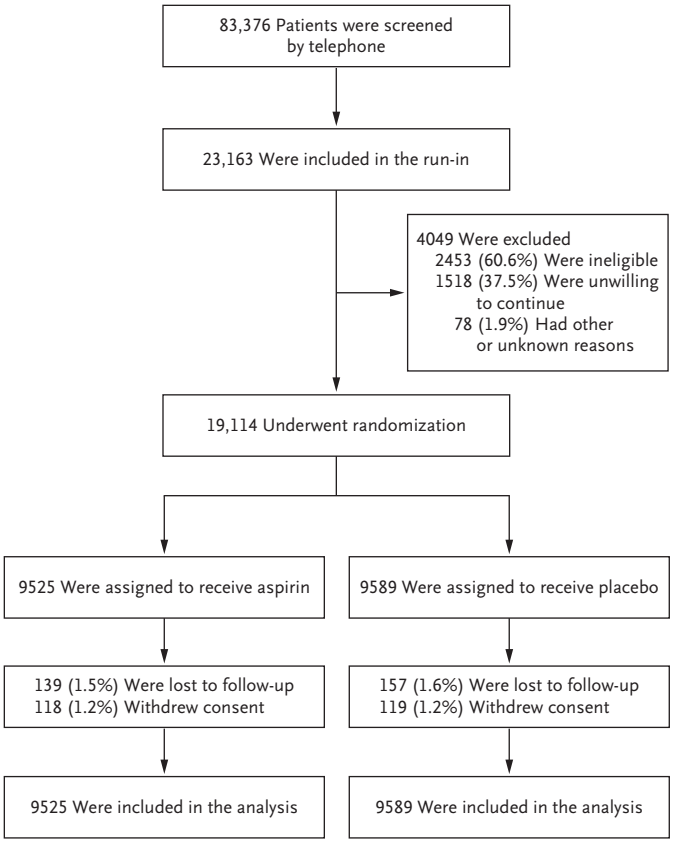

Figure 1. Randomization, Intervention, and Follow-up.

The most common reasons for exclusion from the trial were a history of cardiovascular disease, an adherence rate of less than 80% during the 4-week placebo run-in period, a Modified Mini–Mental State Examination score of less than 78 (on a scale from 0 to 100, with higher scores indicating better function), a score of 4 or 5 for any one of the six basic activities of daily living (bathing, dressing, toileting, transferring, walking, and feeding) on the Katz Index of Independence in Activities of Daily Living (scores for each activity range from 1 [no difficulty] to 5 [unable to do]; a score of 4 indicates severe difficulty in performing the activity), a low hemoglobin level, high blood pressure, or the opinion of the general practitioner or primary care physician. Participants could have more than one reason for ineligibility. For participants who withdrew from the trial, all the information up to the point of withdrawal was included in the analyses. Vital status was obtained in all the participants who were lost to follow-up or withdrew consent.

PRIMARY END POINT

The primary end point of death, dementia, or physical disability occurred in 921 participants in the aspirin group (21.5 events per 1000 person-years) and in 914 in the placebo group (21.2 events per 1000 person-years). The between-group difference was not significant (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11; P=0.79) (Table 2 and Fig. 2).

No significant interactions of subgroups with intervention effects were observed, except for frailty (Figs. S1 and S2 in the Supplementary Appendix). Among participants who had a primary end-point event, death was the most common first event (in 911 participants [50% of the events] at a mean age of 77.5 years), dementia was the next most common (in 549 participants [30% of the events] at a mean age of 77.7 years), and persistent physical disability was the least common (in 375 participants [20% of the events] at a mean age of 77.6 years) (Table 2).

SECONDARY END POINTS

The secondary end point of death from any cause, denoting death as the first, second, or third event to occur in the primary end point, occurred in 558 participants in the aspirin group (12.7 events per 1000 person-years) and in 494 participants in the placebo group (11.1 events per 1000 person-years) (hazard ratio, 1.14; unadjusted 95% CI, 1.01 to 1.29). Because there was no adjustment for multiple comparisons of secondary end points, no inferences can be made regarding differences in mortality between the two groups. The rate of the secondary end point of all dementia was 6.7 events per 1000 person-years in the aspirin group and 6.9 events per 1000 person-years in the placebo group (hazard ratio, 0.98; 95% CI, 0.83 to 1.15) (Table 2 and Fig. 3). The rate of persistent physical disability was 4.9 events per 1000 person-years in the aspirin group and 5.8 events per 1000 person-years in the placebo group (hazard ratio, 0.85; 95% CI, 0.70 to 1.03) (Table 2 and Fig. 3).

The rates of major hemorrhagic events are shown in Table 2. Major hemorrhage occurred in 3.8% of the participants in the aspirin group, as compared with 2.8% of those in the placebo group (hazard ratio, 1.38; 95% CI, 1.18 to 1.62;

Table 1. Demographic Characteristics and Illness History of the Participants at Randomization, According to Prespecified Subgroups and Trial Group.*

Characteristic	Aspirin (N=9525)	Placebo (N=9589)
Age — no. (%)†		
65–73 yr	4719 (49.5)	4823 (50.3)
≥74 yr	4806 (50.5)	4766 (49.7)
Female sex — no. (%)	5373 (56.4)	5410 (56.4)
Country — no. (%)		
Australia	8322 (87.4)	8381 (87.4)
United States	1203 (12.6)	1208 (12.6)
Race or ethnic group — no. (%)‡		
White		
Australia	8169 (85.8)	8193 (85.4)
United States	539 (5.7)	549 (5.7)
Black	451 (4.7)	450 (4.7)
Hispanic	240 (2.5)	248 (2.6)
Other	126 (1.3)	149 (1.6)
Body-mass index§	28.1±4.8	28.1±4.7
Current smoking — no. (%)	352 (3.7)	383 (4.0)
Diabetes mellitus — no. (%)¶	1027 (10.8)	1030 (10.7)
Hypertension — no. (%)‖	7065 (74.2)	7148 (74.5)
Dyslipidemia — no. (%)**	6159 (64.7)	6308 (65.8)
Personal history of cancer — no. (%)	1827 (19.2)	1833 (19.1)
Previous regular aspirin use — no. (%)††	1053 (11.1)	1041 (10.9)
Frailty — no. (%)‡‡		
Not frail	5603 (58.8)	5643 (58.8)
Prefrail	3707 (38.9)	3740 (39.0)
Frail	215 (2.3)	206 (2.1)

* Plus–minus values are means ±SD. There were no significant (P>0.05) differences between the two trial groups; all differences were less than 0.25 SD (if means were compared), and odds ratios were between 0.67 and 1.50 (if proportions were compared).

† The subgroups for age were based on the median age of the participants overall (74 years).

‡ Race and ethnic group were reported by the participants. Other race or ethnic group was defined as any category with less than 200 participants overall, which included Aboriginal or Torres Strait Islander (12 participants), Native American (6), multiple races or ethnic groups (64), Native Hawaiian or Pacific Islander (11), and those who indicated that they were not Hispanic but did not state another race or ethnic group (18).

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ The presence of diabetes was based on participants' report of diabetes mellitus or a fasting glucose level of at least 126 mg per deciliter (≥7 mmol per liter) or receipt of treatment for diabetes.

‖ Hypertension was defined by the receipt of treatment for high blood pressure or a blood pressure of more than 140/90 mm Hg at trial entry.

** Dyslipidemia was defined by the receipt of cholesterol-lowering medication or as a serum cholesterol level of at least 212 mg per deciliter (≥5.5 mmol per liter) in Australia and at least 240 mg per deciliter (≥6.2 mmol per liter) in the United States or as a low-density lipoprotein level of more than 160 mg per deciliter (>4.1 mmol per liter).[13,21]

†† Previous regular aspirin use was defined according to participant-reported regular use of aspirin immediately before the first baseline visit, with a 1-month washout period before randomization.

‡‡ Frailty was categorized on the basis of the adapted Fried frailty criteria, which included body weight, strength, exhaustion, walking speed, and physical activity (see the Supplementary Appendix).[21] The category of prefrail included participants who met one or two criteria, and the category of frail included those who met three or more criteria.

Table 2. Composite Primary End Point, Including the Components, and Secondary End Points of Death, Dementia, Persistent Physical Disability, and Major Hemorrhage.*

End Point	Aspirin (N = 9525)		Placebo (N = 9589)		Hazard Ratio (95% CI)	P Value
	no. of participants with event	*rate per 1000 person-yr*	*no. of participants with event*	*rate per 1000 person-yr*		
Primary end point†	921	21.5	914	21.2	1.01 (0.92–1.11)	0.79
Death from any cause	480	11.2	431	10.0	—	—
Dementia	274	6.4	275	6.4	—	—
Persistent physical disability	167	3.9	208	4.8	—	—
Secondary end points‡						
Death from any cause	558	12.7	494	11.1	1.14 (1.01–1.29)	—
Dementia	283	6.7	292	6.9	0.98 (0.83–1.15)	—
Persistent physical disability	188	4.9	224	5.8	0.85 (0.70–1.03)	—
Major hemorrhagic event	361	8.6	265	6.2	1.38 (1.18–1.62)	<0.001
Clinically significant bleeding	312	7.4	225	5.3	—	—
Hemorrhagic stroke	49	1.2	40	0.9	—	—

* The 95% confidence intervals and P values were not adjusted for multiple comparisons.
† The primary end point was the first occurrence of any one of the three components (death from any cause, dementia, or persistent physical disability).
‡ For the secondary end points, all the participants who had an event at any time during the trial are counted. Other secondary end points included fatal and nonfatal cardiovascular disease, fatal and nonfatal cancer, mild cognitive impairment, and depression. Further results regarding the secondary end points of death, cardiovascular disease (including stroke), and major hemorrhage are reported in two accompanying articles in the *Journal*.[19,20]

P<0.001). Fatal or nonfatal hemorrhagic stroke (including subarachnoid hemorrhage) occurred in 49 participants (0.5%) in the aspirin group and in 40 (0.4%) in the placebo group.

DISCUSSION

In this trial involving community-dwelling older adults who were free from known cardiovascular disease, dementia, or major physical disability, the daily use of 100 mg of enteric-coated aspirin did not differ significantly from placebo in influencing the rates of disability-free survival at a median of 4.7 years. No significant difference was identified regarding the effect of aspirin between the participants in the United States and those in Australia or across a range of other subgroups (prespecified or not prespecified) (Figs. S1 and S2 in the Supplementary Appendix). White participants comprised 91% of the overall trial cohort. Owing to the small number of blacks and Hispanics (including participants who were younger than 70 years of age) and other nonwhites, the applicability of the main findings of the ASPREE trial to these subgroups is unclear.

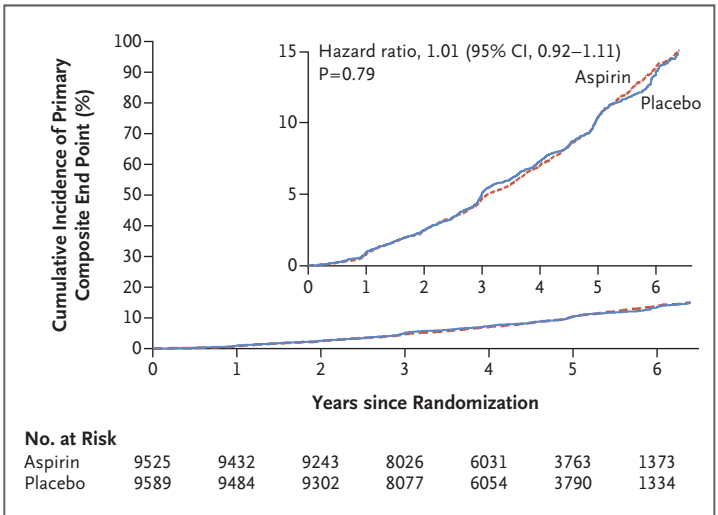

Figure 2. Cumulative Incidence of the Primary Composite End Point.
Shown is the cumulative incidence of the primary composite end point (death from any cause, dementia, or persistent physical disability) according to trial group. First events that counted toward the primary end point during the trial included 911 deaths, 549 cases of dementia, and 375 cases of persistent physical disability. The graph stops at year 6 because only a small number of participants (44 in the aspirin group and 43 in the placebo group) reached year 7. The inset shows the same data on an enlarged y axis.

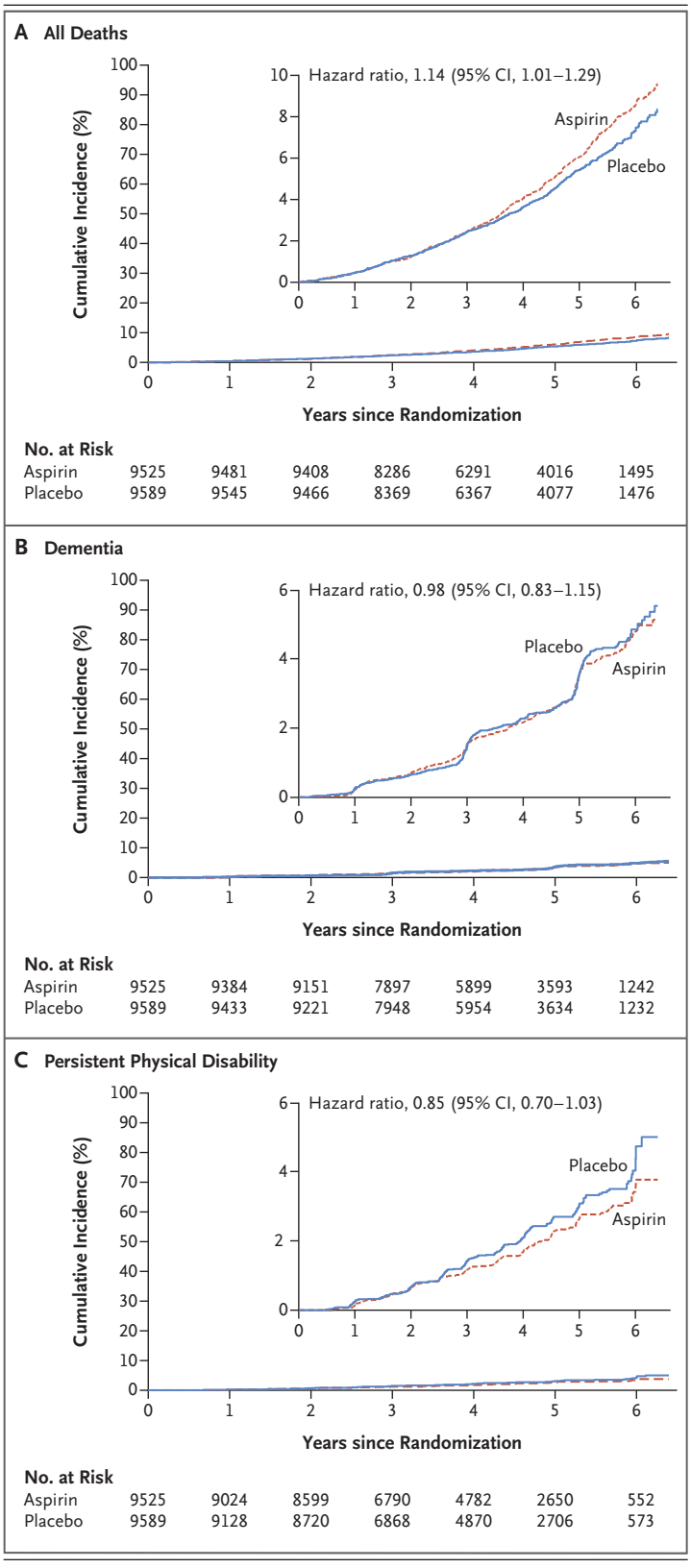

Figure 3. Cumulative Incidence of Death, Dementia, and Persistent Physical Disability.

Shown are the cumulative incidences of all events of death, dementia, and persistent physical disability that were observed during the trial. The 95% confidence intervals were not adjusted for multiple comparisons. Insets show the same data on an enlarged y axis.

Aspirin has become one of the most popular agents used for the primary prevention of cardiovascular disease, largely on the basis of results from studies of secondary prevention of myocardial infarction and ischemic stroke. Large trials investigating primary cardiovascular prevention,[22-32] mainly involving participants younger than those in the ASPREE trial, have not shown a consistent effect of aspirin on cardiovascular outcomes. In many trials, the use of aspirin was accompanied by a higher bleeding risk, without any clear indication of overall benefit or harm.[23,25-28]

Most previous large trials of aspirin have focused on reducing the incidence of cardiovascular events as their primary end point. However, in this age group, the long-term use of a preventive drug may be justified by a prolongation of the time spent in a healthy independent state. An end point that reflects this outcome should integrate the beneficial effects and the serious adverse effects of a preventive agent such as aspirin. By reducing platelet aggregation and thrombotic obstruction, thereby lessening the risk of ischemia in the heart, brain, and other organs, aspirin may be expected to reduce the incidence of disability from various causes. An increased risk of bleeding due to aspirin might have an opposite effect because of intracerebral and gastrointestinal bleeding and their sequelae. In this trial, the primary end point of disability-free survival was considered to integrate the benefits and harms of aspirin and to reflect the fundamental purpose for prescribing a preventive agent in an otherwise healthy elderly population.

Among the events contributing to the composite primary end point, deaths contributed 50% of the total, dementia contributed 30%, and persistent physical disability 20%. When all the events (not just the first event to occur) were taken into account, the rates of dementia were similar in the two groups and there was no evidence of an effect of aspirin on the rate of per-

sistent physical disability. The difference in the rates of death from any cause between the two groups could be a chance finding, and previous primary prevention trials have not shown significantly higher risks of death from any cause with aspirin than with placebo or with no treatment. However, given the concern about potential harm that has been associated with aspirin use in the population enrolled in this trial, we investigated specific causes of death in separate articles, which are now published in the *Journal*.[19,20] As in other trials, the incidence of major hemorrhage was higher in the aspirin group than in the placebo group and amounted to an additional 2.4 serious bleeding events per 1000 person-years of exposure.

With regard to the primary end point in this trial, the lack of effect of aspirin was consistent among all baseline subgroups except for frailty (see the Supplementary Appendix). The effect of frailty is unclear owing to the inconsistent directions of the aspirin effect across the three frailty categories.

Despite the challenges of maintaining participation by older persons in a long-term clinical trial, a relatively high level of adherence to the randomly assigned intervention was maintained and was similar to that in other prevention studies of aspirin.[25,28,29] The limitations of our trial include the relatively short duration of the intervention, which may be important for detecting an effect of aspirin on conditions such as Alzheimer's disease[33,34] and cancer,[5] which have long latencies between their biologic substrates and clinical presentation. The trial results also do not rule out a favorable effect of aspirin if its administration had been commenced at an earlier age or continued for a longer period of time.

Interpretation of the trial results should take into account the low proportion of participants who had been regularly taking low-dose aspirin before entering the trial. This trial did not directly address the question of whether healthy older persons who have been using aspirin for primary prevention should continue or discontinue its use.

In conclusion, these results of the ASPREE trial indicate that, over a median follow-up of 4.7 years, the use of low-dose aspirin in persons 70 years of age or older who did not have cardiovascular disease did not prolong disability-free survival in a predominantly white population.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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REFERENCES

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
2. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
3. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet 2016;388:365-75.
4. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;379:1602-12.
5. Rothwell PM. Aspirin in prevention of sporadic colorectal cancer: current clinical evidence and overall balance of risks and benefits. Recent Results Cancer Res 2013;191:121-42.
6. Sutcliffe P, Connock M, Gurung T, et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. Health Technol Assess 2013;17:1-253.
7. Whitlock EP, Williams SB, Burda BU, Feightner A, Beil T. Aspirin use in adults: cancer, all-cause mortality, and harms: a systematic evidence review for the U.S. Preventive Services Task Force. Evidence syntheses no. 132. Rockville, MD: Agency for Healthcare Research and Quality, 2015 (https://www.ncbi.nlm.nih.gov/books/NBK321643/).
8. Chubak J, Whitlock EP, Williams SB, et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164:814-25.
9. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164:826-35.
10. Li L, Geraghty OC, Mehta Z, Rothwell PM. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017;390:490-9.
11. ASPREE Investigator Group. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. Contemp Clin Trials 2013;36:555-64.
12. Nelson MR, Reid CM, Ames DA, et al. Feasibility of conducting a primary prevention trial of low-dose aspirin for major adverse cardiovascular events in older people in Australia: results from the ASPirin in Reducing Events in the Elderly (ASPREE) pilot study. Med J Aust 2008;189:105-9.
13. McNeil JJ, Woods RL, Nelson MR, et al. Baseline characteristics of participants in the ASPREE (ASPirin in Reducing Events in the Elderly) study. J Gerontol A Biol Sci Med Sci 2017;72:1586-93.
14. Chin AL, Negash S, Hamilton R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer disease. Alzheimer Dis Assoc Disord 2011;25:187-95.
15. Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. Circulation 2017;136(21):e393-e423.
16. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987;48:314-8.
17. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc 1983;31:721-7.
18. Diagnostic and statistical manual of mental disorders, 4th ed.: DSM IV. Washington, DC: American Psychiatric Association, 1994.
19. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018;379:1509-18.
20. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018;379:1519-28.
21. Wolfe R, Murray AM, Woods RL, et al. The aspirin in reducing events in the elderly trial: statistical analysis plan. Int J Stroke 2018;13:335-8.
22. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 1988;296:313-6.
23. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35.
24. Kassoff A, Buzney SM, McMeel JW, et al. Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. JAMA 1992;268:1292-300.
25. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998;351:233-41.
26. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755-62.
27. de Gaetano G, Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Lancet 2001;357:89-95.
28. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293-304.
29. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840.
30. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134-41.
31. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010;303:841-8.
32. Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA 2014;312:2510-20.
33. Gauthier SG. Alzheimer's disease: the benefits of early treatment. Eur J Neurol 2005;12:Suppl 3:11-6.
34. Winblad B, Wimo A, Engedal K, et al. 3-Year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord 2006;21:353-63.