ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

ABSTRACT

BACKGROUND

Diabetes mellitus is associated with an increased risk of cardiovascular events. Aspirin use reduces the risk of occlusive vascular events but increases the risk of bleeding; the balance of benefits and hazards for the prevention of first cardiovascular events in patients with diabetes is unclear.

METHODS

We randomly assigned adults who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer.

RESULTS

A total of 15,480 participants underwent randomization. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%], respectively) or all cancers (897 [11.6%] and 887 [11.5%]); long-term follow-up for these outcomes is planned.

CONCLUSIONS

Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard. (Funded by the British Heart Foundation and others; ASCEND Current Controlled Trials number, ISRCTN60635500; ClinicalTrials.gov number, NCT00135226.)

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*A complete list of the members of the ASCEND Study Collaborative Group is provided in Supplementary Appendix 1, available at NEJM.org.

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It is well established that aspirin use is beneficial for patients with cardiovascular disease, but it is less clear that there is overall benefit in persons who have not yet had a cardiovascular event.[1,2] Patients with diabetes mellitus have a risk of vascular events that is two to three times as high as the risk among those without diabetes,[3] but most of the estimated 400 million persons with diabetes worldwide do not have manifest vascular disease.[4]

The 2009 Antithrombotic Trialists' Collaboration meta-analysis involving 95,000 patients in six primary prevention trials showed that assignment to aspirin use led to a 12% (95% confidence interval [CI], 6 to 18) lower risk of serious vascular events than control.[1] On average, however, the approximate 50% higher risk of bleeding with aspirin use than with control counterbalanced much of the benefit in these low-risk patients. Only approximately 4% of participants in those trials had diabetes, and the lower relative risk among them was similar to that observed among participants without diabetes (as was also observed in the context of secondary prevention). Likewise, the higher relative risk of bleeding with aspirin use than with control was similar among persons with diabetes and those without diabetes.

Since the analyses of the Antithrombotic Trialists' Collaboration, four trials of aspirin use for primary prevention (two specifically involving patients with diabetes[5,6] and two in broader populations[7,8]) have been reported; none showed a clear benefit or reported detailed information regarding bleeding events, so the balance of benefits and risks associated with aspirin use for primary prevention among persons with diabetes remains uncertain. Partly as a result of these studies, there has been speculation that diabetes may be associated with reduced efficacy of the antiplatelet effects of aspirin.[9]

Retrospective meta-analyses of selected randomized trials of mainly low-dose aspirin have suggested that aspirin use may result in an incidence of cancer or death from cancer that is 15 to 20% lower than that with control.[10-13] In particular, reductions of 30 to 40% in the incidence of gastrointestinal cancers (particularly colorectal cancer) were observed, with the effects appearing to increase with more prolonged exposure and with longer follow-up up to 20 years. Data from randomized trials of sufficient size and duration will be useful in assessing any effects of aspirin use on cancer more reliably. We performed the ASCEND (A Study of Cardiovascular Events in Diabetes) randomized trial to assess the efficacy and safety of enteric-coated aspirin at a dose of 100 mg daily, as compared with placebo, in persons who had diabetes without manifest cardiovascular disease at trial entry. Using a factorial design in the same trial, we also randomly assigned the patients to receive a daily regimen of either n–3 fatty acids, administered as 1-g capsules, or placebo, findings that are now reported elsewhere in the *Journal*.[14]

METHODS

TRIAL OVERSIGHT

ASCEND was designed and conducted by independent investigators in the Clinical Trial Service Unit at the University of Oxford (the regulatory trial sponsor). The trial methods, characteristics of the participants, and data analysis plan (including outcome definitions) have been reported previously.[15,16] The protocol (available with the full text of this article at NEJM.org) was approved by the North West Multicenter Research Ethics Committee. The trial was funded by the British Heart Foundation. The aspirin and matching placebo (along with funding for packaging) were provided by Bayer (Germany), and Solvay, Abbott, and Mylan provided the n–3 fatty acid and placebo capsules and some funding for packaging. Bayer (Germany) commented on the design of the trial, and both Bayer and Mylan commented on the draft of the manuscript but had no part in the collection, handling, analysis, or interpretation of the data or in the decision to submit the manuscript for publication. The manuscript was prepared by the writing committee and reviewed and approved for submission for publication by the steering committee. The first and last members of the writing committee vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol and the data analysis plan.

DATA SHARING

Deidentified data about the individual participants are to be shared with the Antithrombotic Trialists' Collaboration for meta-analysis. Requests for data sharing will be handled in line with the data access and sharing policy of the Nuffield Depart-

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ment of Population Health, University of Oxford (www.ndph.ox.ac.uk/about/data-access-policy).

PARTICIPANTS

Men and women at least 40 years of age were considered to be eligible if they had received a diagnosis of diabetes mellitus (any type) and did not have known cardiovascular disease and if there was substantial uncertainty about whether antiplatelet therapy would confer worthwhile benefit. Key exclusion criteria were a clear indication for aspirin or a contraindication to aspirin or the presence of other clinically significant conditions that might limit adherence to the trial regimen for at least 5 years. All the participants provided written informed consent.

PROCEDURES

Potential participants were identified from regional diabetes registers or general practices from around the United Kingdom and were sent a screening questionnaire. Those who returned the questionnaire indicating that they were willing and eligible to participate entered a prerandomization run-in phase, during which placebo aspirin (and placebo n–3 fatty acids) was supplied. Their family doctor was informed of their potential participation, and they were sent a kit to obtain blood and urine samples and to record blood pressure, height, and weight. After this run-in period of 8 to 10 weeks, participants remained eligible if they returned a randomization questionnaire confirming their willingness to continue, they still met the eligibility criteria, and they had adhered to the trial regimen.

Using minimized randomization, we then assigned eligible participants to receive 100 mg of aspirin once daily or a matching placebo tablet[16]; participants were also assigned to receive 1-g capsules containing n–3 fatty acid once daily or a matching placebo capsule. The participants were then mailed a 6-month supply of aspirin or placebo tablets and n–3 fatty acids or placebo capsules, as appropriate.

After randomization, we sent follow-up questionnaires and appropriate tablets and capsules to participants every 6 months until the end of the trial. In these questionnaires, we sought information regarding all serious adverse events (including potential trial outcomes), adherence to the trial regimen, use of nontrial antiplatelet or anticoagulant therapy, nonserious adverse events resulting in discontinuation of the trial regimen, and any symptomatic bleeding episodes for which patients saw a doctor. After a mean follow-up of 2.5 years, we requested blood and urine samples, along with measures of blood pressure and weight, from 1800 randomly selected participants. (Details are provided in the Methods section in Supplementary Appendix 1, available at NEJM.org.)

OUTCOMES

While recruitment was still ongoing, we modified the original primary outcome to include transient ischemic attack in the definition of serious vascular event, a change that was made to increase the statistical power of the trial. Thus, the prespecified primary efficacy outcome was the first serious vascular event, which was defined as a composite of nonfatal myocardial infarction, nonfatal stroke (excluding confirmed intracranial hemorrhage) or transient ischemic attack, or death from any vascular cause (excluding confirmed intracranial hemorrhage). The primary safety outcome was the first occurrence of any major bleeding event, which was defined as a composite of any confirmed intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or any other serious bleeding (i.e., a bleeding event that resulted in hospitalization or transfusion or that was fatal). Secondary outcomes were gastrointestinal tract cancer (overall and excluding those occurring during the first 3 years of follow-up) and the composite of any serious vascular event or any arterial revascularization procedure.

All the reports of possible primary or secondary outcomes were adjudicated centrally by clinicians who were unaware of the trial-group assignments in accordance with prespecified definitions. The data analysis plan prespecified that analyses would be based on all the confirmed events plus unrefuted events (see the Methods section in Supplementary Appendix 1).

STATISTICAL ANALYSIS

The data analysis plan was finalized by the steering committee and was published[16] while all the members were still unaware of the trial results according to group assignment (except for the statistician, who was aware of these assignments and who was not involved in development of the data analysis plan). In addition to revising the definition of serious vascular events to include

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transient ischemic attack, the sample was increased to at least 15,000 participants and the duration of follow-up was increased to at least 7 years to increase the power of the trial. (Details are provided in the Methods section in Supplementary Appendix 1.)

On the basis of an event rate of 1.2 to 1.3% per year, as observed in both groups combined when recruitment was complete, we determined that 7.5 years of the scheduled trial regimen would provide the trial with 90% power, at a P value of less than 0.05, to detect a 15% difference between the treatment groups in the risk of a serious vascular event. The expected number of gastrointestinal tract cancers was estimated to provide the trial with 60% power to detect a 30% lower risk in the aspirin group than in the placebo group during this period, but the prespecified focus for assessing the effects on cancer is 5 and 10 years after the end of the scheduled intervention phase.

We used log-rank methods to conduct intention-to-treat comparisons in time-to-event analyses of the first occurrence of each type of event of interest among participants in the aspirin group as compared with those in the placebo group.[17,18] A two-tailed P value of less than 0.05 was considered to indicate statistical significance for the primary efficacy and safety outcomes. It was prespecified that the combined secondary outcome of serious vascular event or revascularization would be used for any subgroup analyses. We made allowance for multiple hypothesis testing in the interpretation of secondary and exploratory outcomes, with no formal adjustment to the P values. Consequently, the results are reported as point estimates and 95% confidence intervals that have not been adjusted for multiple comparisons, so the confidence intervals should not be used to infer definitive treatment effects within subgroups or with regard to secondary outcomes.

The baseline 5-year risk of vascular events among participants was categorized into three groups — less than 5%, 5% to less than 10%, and 10% or more — with the use of a risk score that had been developed with the use of Poisson regression. Details regarding this and other secondary and exploratory assessments are provided in the data analysis plan[16] and in Supplementary Appendix 1. The Clinical Trial Service Unit at the University of Oxford holds the full database and performed all the analyses.

RESULTS

TRIAL PARTICIPANTS

From June 2005 through July 2011, a total of 15,480 participants underwent randomization. The main prognostic characteristics of the participants were well balanced between the randomized groups (Table 1, and Tables S1 and S2 in Supplementary Appendix 1). Aspirin use before screening was reported by 5508 participants overall (35.6%), but the treating doctor and the participant were sufficiently uncertain about its value to agree to randomization between aspirin and placebo.

At the end of the scheduled follow-up period, complete follow-up data were available for 15,341 participants (99.1%) who had undergone randomization (Fig. S1 and Table S3 in Supplementary Appendix 1). The mean follow-up was 7.4 years, which yielded 57,000 person-years in the aspirin group and 56,945 person-years in the placebo group. Adjudication was complete for more than 90% of the primary and secondary outcomes.

ADHERENCE AND EFFECTS ON VASCULAR RISK FACTORS

The estimated mean adherence (weighted according to person-years at risk for a serious vascular event) to the assigned regimen was 70% in the aspirin group and 70% in the placebo group. During follow-up, adherence to the aspirin regimen declined while the use of nontrial aspirin and other antiplatelet treatment increased. The estimated mean between-group difference in the rate of use of trial aspirin or nontrial aspirin or other antiplatelet treatment was 69 percentage points (Table S4 in Supplementary Appendix 1). The reasons for discontinuation of the trial regimen are shown in Table S5 in Supplementary Appendix 1. The use of nontrial medications (as reported at randomization and after a mean follow-up of 6.7 years) was similar in the two groups (Table S6 in Supplementary Appendix 1).

Table S7 in Supplementary Appendix 1 shows data regarding various vascular risk factors at a mean of 2.5 years after randomization in the selected subgroup of approximately 1000 participants who were broadly representative of the trial population. Findings were similar in the two trial groups except for small differences in the systolic blood pressure and the estimated glomerular fil-

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Table 1. Key Characteristics of the Participants at Baseline.*

Characteristic	Aspirin Group (N=7740)	Placebo Group (N=7740)
Age		
Mean — yr	63.2±9.2	63.3±9.2
Distribution — no. (%)		
<60 yr	2795 (36.1)	2795 (36.1)
60 to <70 yr	3123 (40.3)	3124 (40.4)
≥70 yr	1822 (23.5)	1821 (23.5)
Male sex — no. (%)	4843 (62.6)	4841 (62.5)
White race — no. (%)†	7467 (96.5)	7468 (96.5)
Body-mass index‡		
Mean	30.8±6.2	30.6±6.3
Distribution — no. (%)		
<25	1080 (14.0)	1169 (15.1)
25 to <30	2753 (35.6)	2776 (35.9)
≥30	3665 (47.4)	3536 (45.7)
Unknown	242 (3.1)	259 (3.3)
Smoking status — no. (%)		
Current smoker	639 (8.3)	640 (8.3)
Former smoker	3526 (45.6)	3525 (45.5)
Never smoked	3489 (45.1)	3488 (45.1)
Unknown	86 (1.1)	87 (1.1)
Participant-reported hypertension — no. (%)	4766 (61.6)	4767 (61.6)
Aspirin use before screening — no. (%)	2740 (35.4)	2768 (35.8)
Statin use — no. (%)	5854 (75.6)	5799 (74.9)
Type 2 diabetes — no. (%)§	7282 (94.1)	7287 (94.1)
Duration of diabetes		
Median (interquartile range) — yr	7 (3–13)	7 (3–13)
Distribution — no. (%)		
<9 yr	4337 (56.0)	4322 (55.8)
≥9 yr	2976 (38.4)	2989 (38.6)
Unknown	427 (5.5)	429 (5.5)
Systolic blood pressure		
Mean — mm Hg	136.1±15.2	136.2±15.3
Distribution — no. (%)		
<130 mm Hg	1694 (21.9)	1700 (22.0)
≥130 to <140 mm Hg	1550 (20.0)	1541 (19.9)
≥140 mm Hg	2263 (29.2)	2292 (29.6)
Unknown	2233 (28.9)	2207 (28.5)
Vascular risk score — no. (%)¶		
Low	3128 (40.4)	3136 (40.5)
Moderate	3294 (42.6)	3254 (42.0)
High	1318 (17.0)	1350 (17.4)

* Plus–minus values are means ±SD. Numbers and percentages are shown for categorical variables, and means or medians (with interquartile ranges) for continuous variables. There were no significant differences between the assigned groups. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the participant. Other groups were Indian, Pakistani, or Bangladeshi (1% of participants), African or Caribbean (1%), and other or unknown (1%).

‡ The body-mass index (the weight in kilograms divided by the square of the height in meters) was based on values for height and weight that were reported by the participants.

§ The presence of type 2 diabetes was based on a broad clinical definition involving the age of the participant at the diagnosis of diabetes, the use of insulin within 1 year after diagnosis, and the body-mass index.

¶ We categorized the predicted 5-year risk of serious vascular event (including transient ischemic attack) without the use of aspirin or n–3 fatty acids as follows: low risk as less than 5%, moderate risk as 5% to less than 10%, and high risk as 10% or more.

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tration rate, which may well be chance findings given the multiple comparisons.

EFFECTS ON THE PRIMARY AND SECONDARY VASCULAR OUTCOMES

During the scheduled intervention period, the primary efficacy outcome occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% CI, 0.79 to 0.97; P=0.01) (Fig. 1A). In exploratory analyses, the risk difference was seen mainly in the first 5 years, with no further gain subsequently in the number of participants avoiding an event (Fig. 1B). The effects on the components of the primary efficacy outcome and the secondary outcome of serious vascular event or any arterial revascularization are shown in Figure 2. Prespecified exploratory analyses showed no significant effect of aspirin use, as compared with placebo, on the rate of death from all vascular causes combined, which represented approximately 30% of all deaths (Fig. S2 in Supplementary Appendix 1).

EFFECTS ON THE PRIMARY SAFETY OUTCOME AND OTHER BLEEDING

There was a significant adverse effect of assignment to the aspirin group, as compared with the placebo group, on the incidence of major bleeding (314 participants [4.1%] vs. 245 [3.2%]; rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003) (Fig. 2). Exploratory analyses did not suggest an attenuation of the effect on bleeding over time (Fig. S3 in Supplementary Appendix 1). Of the first major bleeding events, 41.3% were gastrointestinal (of which 62.3% were in the upper gastrointestinal tract, 32.9% were in the lower gastrointestinal tract, 2.2% were perforations, and 2.6% were undetermined), 21.1% were sight-threatening bleeding events in the eye, 17.2% were intracranial bleeding events, and 20.4% were bleeding events in other sites (mainly hematuria and epistaxis that met the definition of major bleeding). The incidence of fatal bleeding events was similar among persons in the aspirin group and among those in the placebo group (19 participants [0.2%] and 16 [0.2%], respectively), as was the incidence of hemorrhagic stroke (25 [0.3%] and 26 [0.3%]) (Table S8 in Supplementary Appendix 1).

EFFECTS ON VASCULAR EVENTS AND BLEEDING ACCORDING TO BASELINE CHARACTERISTICS

In exploratory analyses, the proportional effects of aspirin use on the combined outcome of serious vascular events or revascularization and on the safety outcome of major bleeding did not show clear evidence of variation according to particular baseline characteristics (with allowance for multiple comparisons). In particular, neither outcome varied according to group assignment with regard to n–3 fatty acids or to the vascular risk group at baseline (Figs. S4 and S5 in Supplementary Appendix 1). Figure 3 shows that the incidence of a major bleeding event increased with vascular risk. Substantial uncertainty around the observed number of events caused and avoided results from small numbers and differences in adherence. Figure S6 in Supplementary Appendix 1 shows the predicted absolute effects with extrapolation to full adherence to the trial regimen.

EFFECTS ON OTHER VASCULAR AND MICROVASCULAR OUTCOMES

Results of exploratory analyses of the effects of aspirin use on other vascular and selected microvascular outcomes are shown in Figure S7 and Table S9 in Supplementary Appendix 1. The results regarding the vascular events show trends that are generally similar to those regarding serious vascular events. There was no apparent effect of aspirin use on selected microvascular events.

EFFECTS ON CANCER AND OTHER NONVASCULAR OUTCOMES

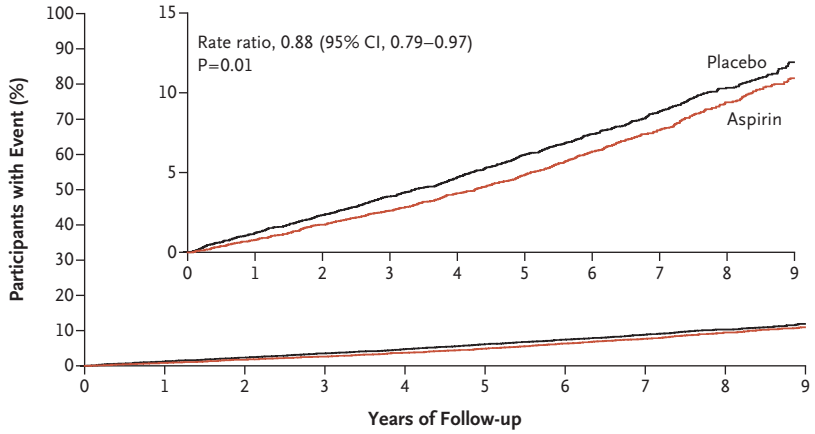
There was no between-group difference in the risk of gastrointestinal tract cancer, nor was there a suggestion of an effect emerging with longer follow-up (Fig. S8 in Supplementary Appendix 1). The trial groups also did not differ significantly with regard to the risk of fatal or nonfatal cancer overall or at particular sites (Table 2, and Fig. S9 in Supplementary Appendix 1) or with regard to the risks of death overall or death from cancer or from all nonvascular causes (Fig. S2 in Supplementary Appendix 1). Searchable tabulations of the serious adverse events (fatal and nonfatal combined) are provided in Supplementary Appendix 2, available at NEJM.org. They are grouped on the basis of the *Medical Dictionary for Regulatory Activities*, version 14.0, classification system, according to system organ class.

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DISCUSSION

In this trial involving persons who had diabetes without manifest cardiovascular disease, assignment to the use of aspirin at a dose of 100 mg daily for 7.4 years resulted in a risk of serious vascular events that was 12% lower than that with placebo but also in a risk of major bleeding that

A First Serious Vascular Event



No. at Risk										
Placebo	7740	7618	7486	7342	7188	7001	5771	3890	2200	1430
Aspirin	7740	7655	7536	7404	7252	7096	5825	3966	2222	1428
Cumulative benefit per 1000 participants in aspirin group		4±2	6±2	9±3	10±3	13±4	11±4	12±5	9±6	10±7

B First Serious Vascular Event, According to Year of Follow-up

Year of First Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
<3	201 (2.6)	269 (3.5)	0.74 (0.62–0.89)	
3 to <5	169 (2.3)	198 (2.7)	0.85 (0.69–1.04)	
≥5 to <7	180 (2.5)	171 (2.4)	1.04 (0.84–1.28)	
7	108 (2.7)	105 (2.7)	1.02 (0.78–1.33)	
All	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**

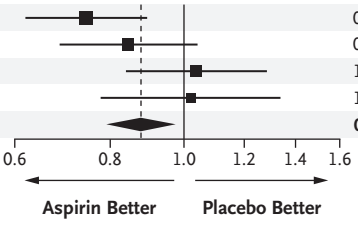


Figure 1. First Serious Vascular Event during Follow-up.

Panel A shows a Kaplan–Meier plot of the first serious vascular event (a composite of nonfatal myocardial infarction, nonfatal ischemic stroke or transient ischemic attack, or death from any vascular cause, excluding confirmed intracranial hemorrhage) during follow-up. The numbers of participants at risk at the start of each year of follow-up are shown, along with the cumulative number (±SE) of participants per 1000 in the aspirin group as compared with the placebo group who avoided events. The inset shows the same data on an expanded y axis. Panel B shows the rate ratios for the first serious vascular event among the participants in the aspirin group, as compared with those in the placebo group, according to the period of follow-up. The numbers at risk declined with each period of follow-up because of censoring, so the percentages are the number of events as a proportion of the number at risk at the start of each period. For each period of follow-up, rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals (not adjusted for multiple comparisons), and the dashed vertical line indicates the overall rate ratio for the effect of aspirin use on the first serious vascular event. For the prespecified composite period of follow-up, the rate ratio and corresponding 95% confidence interval are represented by a diamond. Squares or a diamond to the left of the solid vertical line indicate a benefit with aspirin use, but the comparison was significant (P<0.05) only if the horizontal line or diamond does not overlap with the solid vertical line. The test for trend across years was significant (χ^2=6.24; P=0.01).

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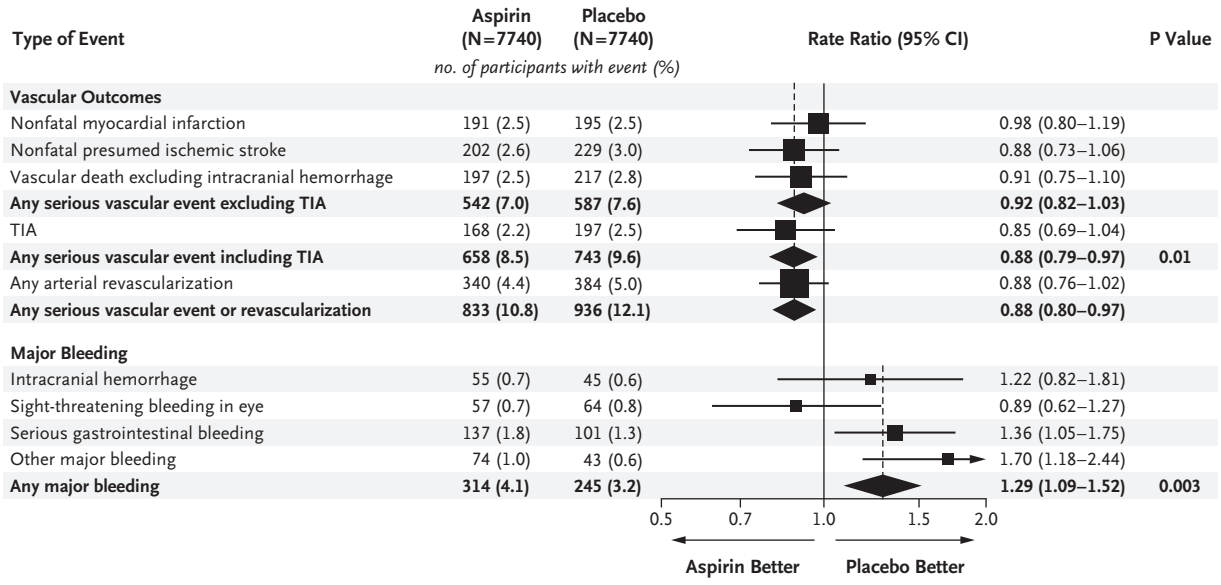


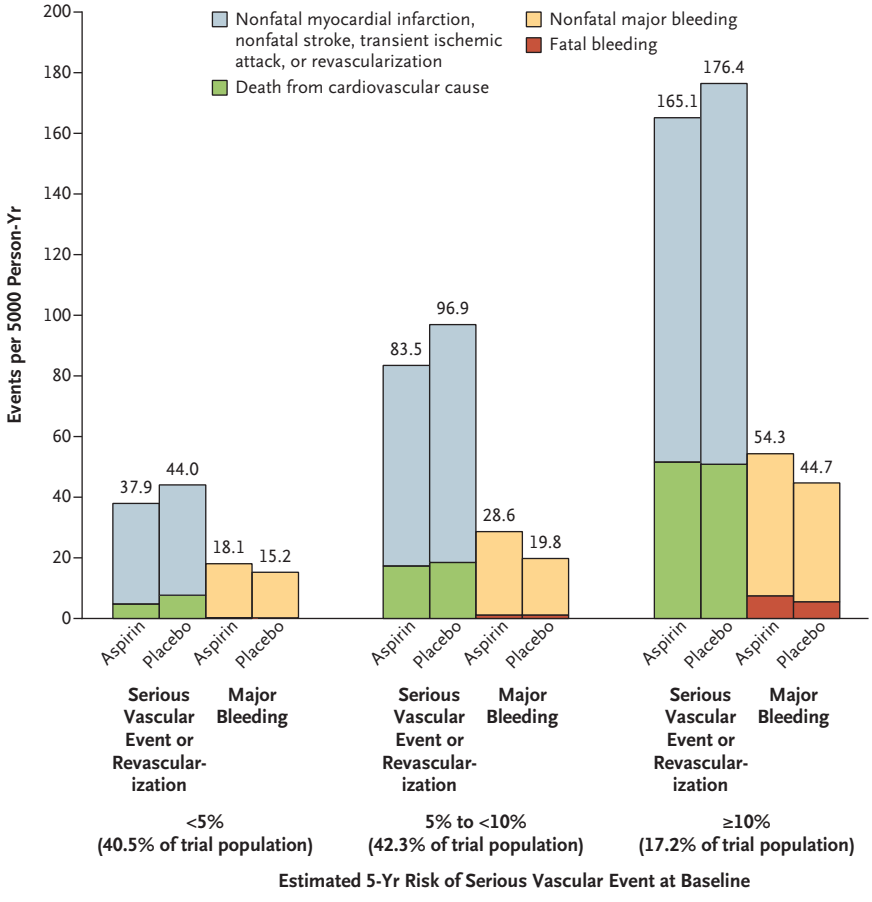
Figure 2. Effect of Assignment to Aspirin Group on Components of Serious Vascular Events, the Combined Outcome of Serious Vascular Event or Revascularization, and Major Bleeding and Its Components.

The primary outcome was a serious vascular event (a composite of nonfatal myocardial infarction, nonfatal ischemic stroke or transient ischemic attack [TIA], or death from any vascular cause, excluding confirmed intracranial hemorrhage). Secondary outcomes were a serious vascular event or any coronary or noncoronary revascularization procedure. A single participant may have had multiple events and therefore may contribute information to more than one row. The size of each square for the rate ratio is proportional to the amount of statistical information that was available, the horizontal lines represent 95% confidence intervals, and the dashed vertical line indicates the overall rate ratio for the effect of aspirin use on the first serious vascular event. An arrow on the horizontal line indicates that the confidence interval exceeds the graph area. For composite outcomes, rate ratios and their corresponding 95% confidence intervals are represented by diamonds. Bold entries with diamonds show totals for all data listed above them. The effect of aspirin use on the components of the primary safety outcome of major bleeding event (a composite of intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other major bleeding event) is shown with the use of the same graphic conventions.

was 29% higher. The lower risk of serious vascular events is similar to the risk that was reported previously in the Antithrombotic Trialists' Collaboration meta-analysis of primary prevention trials of similar doses of aspirin (which used slightly different outcome definitions; see the Methods section in Supplementary Appendix 1).[1] In contrast to those previous trials, there were high rates of the use of cardioprotective treatments among the participants in ASCEND, with the majority of participants taking statins and blood pressure–lowering therapy. Hence, the present trial provides a direct assessment of the balance of the benefits and hazards of aspirin use in a contemporary context.

In our trial, factors such as the large number of participants and clinical outcomes, long duration of follow-up, the randomized, blinded design of the trial, and the almost complete follow-up of the participants who underwent randomization have allowed reliable detection of these moderate but important effects on the incidence of vascular events and on both the severity and incidence of bleeding. Our findings do not support the hypothesis that persons with diabetes have a resistance to aspirin.[9] Although the proportional effects of aspirin use are likely to be generalizable to the wider population of persons with diabetes, the absolute event rates and adherence rates reflect this population of persons with well-treated diabetes. Overall, on the basis of the absolute percentage differences between the groups in the incidence of serious vascular events (1.1 percentage points lower in the aspirin group than in the placebo group) and in bleeding events (0.9 percentage points higher in the aspirin group), 91 patients would need to be treated to avoid a serious vascular event over a

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No. of Events per 5000 Person-Yr in Aspirin Group			
Serious vascular events avoided	5.7±3.7	11.2±5.4	4.9±12.9
Serious vascular events or revascularizations avoided	6.1±4.2	13.4±6.3	11.3±14.3
Major bleeding caused	2.8±2.6	8.9±3.2	9.6±7.5

Figure 3. Observed Absolute Effect of Assignment to Aspirin Group on Serious Vascular Events or Revascularization and on Major Bleeding, According to Vascular Risk.

Shown is the observed absolute incidence of serious vascular events or revascularization and of major bleeding events in the aspirin group, as compared with the placebo group, according to the three baseline levels of vascular risk (predicted 5-year risks of a serious vascular event, with low risk defined as <5%, moderate risk as 5% to <10%, and high risk as ≥10%), with data expressed as numbers of events per 5000 person-years. Plus–minus values are means ±SE.

period of 7.4 years, and 112 to cause a major bleeding event.

These results of intention-to-treat analyses tend to underestimate the effect of actual aspirin use, both with respect to events avoided and bleeding events caused owing to a lack of full adherence to the regimen during the trial. Exploratory analyses comparing participants at different levels of vascular risk extrapolated the rate ratios in the intention-to-treat analysis to full adherence and assumed that the proportional effects on the incidence of serious vascular events and bleeding were the same across different levels of vascular risk. The results of these analyses provide a more reliable estimate of the absolute differences in the event rates resulting from aspirin use by applying the extrapolated overall rate ratios to the event rates with placebo in each risk group. On the basis of these assumptions, the predicted number of serious vascular events that would be avoided by participants actually taking aspirin was closely balanced by the predicted

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Table 2. Effect of Aspirin Use on the Incidence of Site-Specific Fatal or Nonfatal Cancer.*

Cancer Type	Aspirin Group (N=7740)	Placebo Group (N=7740)	Rate Ratio (95% CI)
	no. of participants (%)		
Gastrointestinal tract cancer	157 (2.0)	158 (2.0)	0.99 (0.80–1.24)
Other gastrointestinal cancer†	87 (1.1)	82 (1.1)	1.06 (0.78–1.43)
Respiratory cancer	101 (1.3)	103 (1.3)	0.98 (0.74–1.29)
Genitourinary cancer	332 (4.3)	294 (3.8)	1.13 (0.97–1.32)
Hematologic cancer	88 (1.1)	86 (1.1)	1.02 (0.76–1.38)
Breast cancer	97 (1.3)	96 (1.2)	1.01 (0.76–1.34)
Melanoma	50 (0.6)	59 (0.8)	0.85 (0.58–1.23)
Other cancer	25 (0.3)	30 (0.4)	0.83 (0.49–1.41)
Unspecified cancer	26 (0.3)	31 (0.4)	0.84 (0.50–1.41)
Any cancer‡	897 (11.6)	887 (11.5)	1.01 (0.92–1.11)

* The 95% confidence intervals were unadjusted for multiple comparisons. A single participant may have had multiple cancers.
† Other gastrointestinal cancer includes hepatobiliary and pancreatic cancers.
‡ Any cancer excludes nonfatal nonmelanoma skin cancer and nonfatal recurrence of a cancer that had occurred before randomization.

number of major bleeding events caused, even among persons who had a 5-year vascular risk of 10% or more (Fig. S6 in Supplementary Appendix 1). A recent analysis suggesting a greater benefit of low-dose aspirin use on the incidence of vascular events among persons with a body weight of less than 70 kg was not confirmed in exploratory subgroup analyses (and, indeed, a trend in the opposite direction was observed).[19]

The assessment of the balance between the benefit and harm of aspirin use in the context of primary prevention is complicated by the difficulty of comparing the severity of the vascular events avoided and the bleeding events caused. For example, although transient ischemic attacks are minor in themselves, they are associated with increased risks of subsequent stroke and cognitive impairment.[20] Approximately half the excess of bleeding was in the gastrointestinal tract, with approximately one third in the upper gastrointestinal tract. However, even near the end of the trial in 2016, only approximately one quarter of participants were receiving proton-pump inhibitors (PPIs). It is possible that bleeding rates among aspirin users might be lower if PPIs were routinely used in these persons, provided that longer-term trials of PPIs[21,22] confirm the substantial reductions in the incidence of bleeding in the upper gastrointestinal tract that has been seen in short-term studies,[23] as well as confirming long-term safety.

Several meta-analyses of selected randomized trials of generally low-dose aspirin have suggested that aspirin use might reduce the risk of cancer — in particular, gastrointestinal tract cancer — by up to one third during long-term follow-up, with effects becoming apparent approximately 3 years after randomization.[10,12,13,24] However, despite more than 7 years of aspirin treatment and follow-up in ASCEND, we found no evidence of a reduction in the incidence of gastrointestinal tract cancer or of cancer at any other site, even during the later years of follow-up. These analyses had limited statistical power to detect the hypothesized effects, so follow-up is being continued through central registries.

In conclusion, the use of low-dose aspirin led to a lower risk of serious vascular events than placebo among persons with diabetes who did not have evident cardiovascular disease at trial entry. However, the absolute lower rates of serious vascular events were of similar magnitude to the absolute higher rates of major bleeding, even among participants who had a high vascular risk. The use of low-dose aspirin did not result in a lower risk of gastrointestinal tract cancer or other

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cancer over the mean follow-up of 7.4 years, but further follow-up is needed to assess any longer-term effects on cancer reliably.

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APPENDIX

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