Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Jones WS, Mulder H, Wruck LM, et al. Comparative effectiveness of aspirin dosing in cardiovascular disease. N Engl J Med 2021;384:1981-90. DOI: 10.1056/NEJMoa2102137

Supplementary Appendix

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Supplementary Methods

Study Organization

The statistical and data coordinating center at Duke Clinical Research Institute (Durham, NC) coordinated data collection and query resolution and performed all statistical analyses. The authors vouch for the accuracy and completeness of the data and all the analyses, as well as for the fidelity of this report to the study protocol and statistical analysis plan. The first author prepared the first draft of the manuscript, and all authors made the decision to submit the manuscript for publication.

The initial protocol was posted for public review and comment in July 2015, and questions about eligibility criteria were voted upon by key stakeholders, including patient-partners, site investigators, and research personnel. The final protocol was approved by the trial executive committee, the Duke University institutional review board (coordinating center), and by the institutional review boards providing oversight at participating centers. Prior to initiation, the United States Food and Drug Administration provided a letter to state that the clinical trial met the criteria for Investigational New Drug exemption in CFR 312.2(b).

Role of the Funder/Sponsor: PCORI approved the design and conduct of the study. They had no role in collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Inclusion/Exclusion Criteria

The eligibility criteria for established ASCVD was defined by any of the following: (1) prior myocardial infarction; (2) prior coronary revascularization procedure (percutaneous coronary intervention or coronary-artery bypass grafting surgery); (3) prior coronary angiography demonstrating ≥75% stenosis of at least 1 epicardial coronary artery; or (4) history of chronic ischemic heart disease, coronary artery disease, or ASCVD. Exclusion criteria included a history of significant allergy to aspirin, history of gastrointestinal bleeding within 12 months, bleeding disorder that precluded aspirin use, current or planned use of an oral anticoagulant or ticagrelor, and female patients who were pregnant or nursing. There were no exclusion criteria for upper age limit, comorbid conditions, or other concomitant medications.

Enrichment Criteria

Eligible patients were required to have at least 1 enrichment criterion: age ≥65 years, serum creatinine ≥1.5 mg/dL, diabetes mellitus, current cigarette smoking, cerebrovascular disease, peripheral artery

disease, heart failure (systolic or diastolic), left ventricular ejection fraction <50%, systolic blood pressure ≥140 mm Hg, or low density lipoprotein cholesterol ≥130 mg/dL.

Recruitment Strategies

After applying the computable phenotype at enrolling centers, approximately 650,000 potentially eligible participants were identified for the study. Multimodal 'high-touch' (i.e., traditional, in-person contact) and 'low-touch' (i.e., electronic mail, standard mail, electronic health record messages, telephone calls) methods were utilized to approach potential participants for enrollment. Potentially eligible participants were provided a personalized access code that both allowed them access to the online patient portal and linked them to the enrolling health system. The patient portal was available in English and Spanish. Once connected to the patient portal, the patient was able to read about the study, watch an informational video, answer eligibility questions, answer 5 comprehension questions about the reasons and commitment to participate, and finally to sign the electronic informed consent form. In order to accommodate study participants who did not have access to the internet or did not feel comfortable with the technology, 'non-internet' participation was allowed and study personnel at enrolling centers facilitated enrollment using electronic tablets at clinic visits.

Retention Efforts

During the course of the study, newsletters were distributed to the participants in which Adaptors wrote pieces that covered topics such as study medication adherence, interpretation of primary prevention studies, importance of completing study visits, and how to disseminate results. Additionally, all-site teleconferences were held monthly that provided study updates, addressed key questions, and provided a forum for investigators and researchers to discuss best practices as it related to the conduct of the study.

End Point Ascertainment and Validation

Programming algorithms were developed by the data coordinating center and distributed to each entity to identify nonfatal outcomes using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) and Procedure Coding System (ICD-10-PCS)* codes. Death was captured from electronic health records, linkage to private and public health insurance claims data, and notifications from participants' friends and family members. In some instances, participants had an end point prior to withdrawal of consent, and these end points were counted in the main analysis. In other instances, study centers were granted permission to ascertain death in those participants who withdrew consent from the study. Thus, the number of participants with data available for the primary analysis included some

participants who withdrew consent. Vital status was confirmed prior to study completion via multiple methods including electronic health record review, telephone calls from the Call Center, and internet searches. Participant-reported hospitalizations required confirmation by data from additional sources to ensure that these events qualified as study outcomes. In the event that patient-reported hospitalizations could not be reconciled with claims/codes from the data sources, medical records were obtained and reviewed by clinicians at the clinical coordinating center to confirm or refute the outcomes.
According to a pre-specified end point validation plan that was submitted to PCORI in 2017, we planned to adjudicate 225 non-fatal events, which turned out to be more than one-third of the overall non-fatal events. Prior literature suggested that myocardial infarction events that were reported by site investigators or were identified by claims data had high levels of agreement with formal clinical end point adjudication. Stroke events, because of some nuances with stroke symptoms, had not correlated as well with formal adjudication in prior studies. Clinicians at the Duke Clinical Research Institute reviewed hospital records for 194 (of planned 225) non-fatal end points (MI, stroke, major bleeding) that had been identified in the electronic health record data and performed formal adjudication of these events. The positive predictive value for these end points was 90.3% for MI, 71.6% for stroke, and 92.7% for major bleeding. When stroke was listed as the primary diagnosis code for hospitalizations, the positive predictive value was very high. The lower positive predictive value that was reported (71.6%) was mostly due to the fact that "stroke" was listed in a position other than the primary diagnosis for hospitalizations, and this represented patients with prior strokes rather than a mis-classification of stroke as a reason for hospitalization.

Aspirin Formulation After Randomization

A total of 14,117 participants answered the question "Is your aspirin tablet enteric coated?" Of these responses, 3185 (22.6%) responded "Don't Know," 7371 (52.2%) responded "Yes," 3318 (23.5%) responded "No," and 243 (1.7%) left the form blank.

Secondary Analyses and Subgroup Analyses

The treatment effect on quality of life outcomes over time was assessed using a mixed model with random slope and intercept. Model-based mean scores with standard error are presented at 6 month increments up to 2 years post-randomization. Treatment effects on the primary outcome and any interactions were tested in pre-specified subgroups that included age, race, sex, diabetes mellitus, chronic kidney disease (defined as serum creatinine >1.5 mg/dL), and use of oral P2Y12 inhibitor at baseline. Age was modeled as a natural cubic spline with 4 knots and the treatment effect was presented at 2 values of

age (60 and 70). An additional subgroup analysis was performed post-hoc evaluating the treatment effect of aspirin dose in patients with body weight < 70 kg and >= 70 kg (added to Figure S7).

Censoring Rules

If a participant did not experience an effectiveness or safety outcome, they were censored at the earlier of study end date, date of withdrawal of consent, death (non-fatal outcomes), or maximum follow-up time point determined from any of the following data sources: EHR, CMS, private health insurance claims, or the patient portal (last point of contact). The censoring date for EHR data was the site-specific censoring date, which was determined by the PCORnet Distributed Research Network Operations Center based on the availability and completeness of the data. For most sites, this was June 30, 2020. The censoring date for CMS was the minimum of the end of enrollment in fee-for-service or March 31, 2020. The censoring date for private health insurance claims was the minimum of the end of enrollment or June 30, 2020.

Sample Size Calculations

The original trial sample size of 20,000 participants was chosen to provide 85% power to detect a 15% relative risk reduction assuming a primary effectiveness outcome rate of 5% per year in the higher-risk arm. In 2017, the sample size was re-evaluated by the Coordinating Center (with PCORI oversight) using data on trial recruitment rates and blinded, aggregate event rates, and the trial size was reduced to 15,000 participants. The decision to reduce sample size in 2017 was based on a number of factors including slower than expected recruitment, longer duration of follow-up for participants who joined early in the process of the study, and a fixed amount of funding that would not permit longer enrollment. Utilizing blinded data with updated event-rate assumptions in 2019, study follow-up was extended for an additional 6 months due to lower-than-expected aggregate event rates. Final power calculations determined that a trial with 15,000 participants would have at least 88% power to detect a 15% relative risk reduction in the primary outcome, assuming an annualized event rate of 4.6% in the higher-risk arm and a maximum follow-up of 50 months.

Sensitivity Analyses

We performed a series of sensitivity analyses to assess robustness of primary analyses.

- Prior aspirin dose (Table S8): We conducted a 10-day landmark analysis excluding events occurring in the first 10 days following randomization to account for the expected time period of washout from the pre-randomization aspirin dose. If a participant experienced an event during the first 10 days of the trial, they were not included in the analysis. For all other participants, their time to event or censor was adjusted by 10 days.

- Nonadherence (Table S8): We replaced the randomized treatment variable with time-varying participant-reported aspirin dose in the primary analysis Cox model. We used all reported information from one completed visit to the next. Dose was only missing if the participant never reported current aspirin dose after randomization (4.0% in 81 mg arm, 5.8% in 325 mg arm). These participants were excluded from the model. We assumed that participants were continuing the last reported dose until reported otherwise. Missing visits would have resulted in a lag in timing of dose switching included in the model. We may have also missed dose switching that occurred after last reported aspirin dose (8.3% of 81 mg arm and 9.9% of 325 mg arm were alive at the end of the study but did not complete an end-of-study visit).
- COVID-19: We ran the primary analysis Cox model with all follow-up censored for the primary efficacy endpoint on December 31, 2019 the original study end date and prior to COVID-19 entering the United States.
- Under-reporting of events (Figure S7): We conducted two sets of sensitivity analyses to assess robustness of primary analysis inference to underreporting of the primary endpoint due to participants moving or seeking care outside of the CDM health system.
    - We repeated the primary analysis modifying the censoring rules for EHR data such that the EHR censoring date was the last date the patient encountered the health system. This included inpatient and outpatient visits, labs, vitals and prescription medication fills. All other censoring dates remained the same.
    - We conducted a tipping point analysis to identify how many events would have to have been missed to achieve significance. For participants at risk of under-reporting as defined by available endpoint data, events were added sequentially. For each iteration, 1000 events were randomly generated from a Weibull model fit to the entire ITT population. Event times generated beyond the participant's censoring time were censored and not imputed. A Cox model as specified for the primary analysis was fit to the resulting dataset and treatment effect hazard ratio estimated, with standard errors adjusted using standard multiple imputation combining rules. Events were added until the lower limit of the 95% CI for the HR of the treatment effect crossed 1.0 or the number of participants at risk of underreporting was reached.
- Misclassification of events (Figure S8): We conducted two sets of sensitivity analyses to assess robustness of primary analysis inference to misclassification of events based on electronic phenotype definitions.
    - We repeated the primary analysis modifying the code-based definitions of primary endpoints to include codes in any position.

- We conducted a tipping point analysis to identify combinatinos of positive predictive value (PPV) and negative predictive value (NPV) that would have changed primary inference. PPV and NPV were varied from 0.5 to 1 to reclassify primary endpoints for those participants at risk of misclassification as defined by available endpoint data. For each combination of PPV and NPV, the corresponding number of reclassified events were imputed 1000 times. Reclassified events were randomly selected and set to non-events. Reclassified non-events were generated from a Weibull model fit to the entire ITT population. A Cox model as specified for the primary analysis was fit to the resulting dataset and treatment effect hazard ratio estimated, with standard errors adjusted using standard multiple imputation combining rules. The heat map represents p-values obtained from the Cox models.

Reasons for Discontinuation

We collected the reasons for permanent discontinuation in participants who reported this in the patient portal or via the Call Center. In the group randomized to 81 mg of daily aspirin, 65 (18.6%) reported patient preference, 74 (21.2%) reported need for oral anticoagulant, 18 (5.2%) reported bleeding or bruising, 102 (29.2%) reported other medical condition, 33 (9.5%) cited the primary prevention studies or ACC/AHA guidelines, and 57 (16.3%) reported “Other” as reasons to discontinue aspirin. In the group randomized to 325 mg of daily aspirin, 84 (15.9%) reported patient preference, 110 (20.8%) reported need for oral anticoagulant, 24 (4.5%) reported bleeding or bruising, 204 (38.6%) reported other medical condition, 36 (6.8%) cited the primary prevention studies or ACC/AHA guidelines, and 70 (13.3%) reported “Other” as reasons to discontinue aspirin.

Table S1. Site Enrollment and Number of Participants Randomized to Each Study Group

Site	Total Participants Randomized	Randomized to 81mg	Randomized to 325mg
Vanderbilt University	2,288	1,126	1,162
Duke University	1,684	856	828
Ochsner	774	398	376
University of Kansas Medical Center	738	338	400
University of Florida Gainesville	694	342	352
University of Pittsburgh	678	326	352
University of Iowa	606	306	300
UNC Chapel Hill	585	298	287
Medical College of Wisconsin	524	271	253
Montefiore Medical Center	516	259	257
Mayo Clinic	500	250	250
University of Utah	464	220	244
Essentia Health	449	228	221
University of Michigan	434	215	219
Wake Forest	409	209	200
Johns Hopkins	370	188	182
HealthCore	357	177	180
Marshfield Clinic	321	174	147
Intermountain Medical Center	290	136	154
Penn State University	275	140	135
Weill Cornell Medical College	258	138	120
University of Chicago	245	115	130
Northwestern Medical	203	101	102

Indiana University	180	98	82
Baylor Scott and White	179	100	79
University of Missouri	178	92	86
University of Nebraska Med Ctr	139	71	68
University of California Los Angeles	131	64	67
Rush	113	55	58
Allina Health System	110	52	58
Ohio State University	91	42	49
Temple University	86	46	40
Florida Hospital	66	33	33
University of Texas Health Sciences San Antonio	35	19	16
New York University Langone Medical Center	34	14	20
University of Texas Southwestern	26	16	10
Mount Sinai Health System	22	13	9
Orlando Health	11	6	5
Bond Community Health Center	8	5	3
Tulane	5	3	2
Grand Total	**15,076**	**7,540**	**7,536**

Table S2. Expected study encounters and cumulative encounter completion rate

	Overall
Expected	123978
Died before end of follow-up	672
Withdrew consent before end of follow-up	614
Cumulative visit completion rate*	
0%	684 (5%)
1-25%	754 (5%)
26-50%	1701 (11%)
51-75%	4400 (29%)
75-99%	6523 (43%)
100%	1013 (7%)

*Cumulative visit completion rate is reported at the participant level and reflects the % of expected visits for a given participant that were completed. Expected visits are defined using the time from randomization to end of study and the randomized follow-up strata. Values sum to 15075 due to one participant dying prior to the week 1 visit.

Table S3. Data Availability for study participants during the course of the study

	Data sources available			
Scenario	**Self-report**	**EHR**	**Claims (CMS or Private)**	**N**
1	X			39
2	X	X		8591
3	X		X	275
4	X	X	X	4456
5		X		1402
6			X	84
7		X	X	212
8				17
Overall				15076

"Data available" indicates that data was available for at least half of available follow-up for each data source.

Table S4. Data source where primary effectiveness end point was captured, based on treatment group

	81 mg dose (N=7540)	325 mg dose (N=7536)
Number of participants with primary effectiveness endpoint	590	569
Event source[1]		
EHR/claims/PRO	5/590 (0.8%)	7/569 (1.2%)
EHR/PRO	16/590 (2.7%)	16/569 (2.8%)
Claims/PRO	8/590 (1.4%)	1/569 (0.2%)
EHR/Claims	145/590 (24.6%)	168/569 (29.5%)
EHR only	264/590 (44.7%)	242/569 (42.5%)
Claims only	97/590 (16.4%)	90/569 (15.8%)
PRO only*	55/590 (9.3%)	45/569 (7.9%)

*For end points that were captured only by patient-report, an end point reconciliation process was used and health information was collected to support the end point confirmation.

Table S5. Characteristics of participants at baseline

Characteristics	81 mg Aspirin (N=7540)	325 mg Aspirin (N=7536)
Age, median, (25th, 75th), yrs	67.7 (60.7, 73.6)	67.5 (60.7, 73.5)
Female sex, no. (%)	2307 (30.6%)	2417 (32.1%)
Weight, median (25th, 75th), kg	90.0 (78.6, 103.6)	90.0 (78.2, 104.1)
Race, no. (%)		
White	6014 (79.8%)	5976 (79.3%)
Black or African American	664 (8.8%)	647 (8.6%)
Asian	82 (1.1%)	64 (0.8%)
American Indian or Alaska Native	69 (0.9%)	45 (0.6%)
Multiple races	71 (0.9%)	63 (0.8%)
Prefer not to say	435 (5.8%)	545 (7.2%)
Other	205 (2.7%)	196 (2.6%)
Ethnicity, no. (%)		
Hispanic	249 (3.3%)	232 (3.1%)
Non-Hispanic	6816 (90.4%)	6737 (89.4%)
Prefer not to say	475 (6.3%)	567 (7.5%)
Medical history, no. (%)		
Prior myocardial infarction	2674 (35.6%)	2631 (35.0%)
Prior coronary revascularization	4034 (53.6%)	3943 (52.4%)
Prior percutaneous coronary intervention	3005 (40.0%)	2941 (39.1%)
Prior coronary artery bypass graft surgery	1786 (23.8%)	1741 (23.2%)
Hypertension	6264 (83.3%)	6248 (83.1%)
Dyslipidemia	6472 (86.1%)	6474 (86.1%)
Diabetes mellitus	2820 (37.5%)	2856 (38.0%)
Atrial fibrillation	605 (8.0%)	628 (8.4%)
Cerebrovascular disease	1324 (17.6%)	1300 (17.3%)
Congestive heart failure	1718 (22.8%)	1786 (23.8%)
Chronic obstructive pulmonary disease/Asthma	1339 (17.8%)	1439 (19.1%)
Chronic kidney disease	1315 (17.5%)	1333 (17.7%)
Peripheral artery disease	1706 (22.7%)	1787 (23.8%)
Prior history of bleeding		
Significant bleeding disorder	80 (1.1%)	96 (1.3%)
Prior significant gastrointestinal bleed	455 (6.1%)	495 (6.6%)
Prior intracranial hemorrhage	98 (1.3%)	110 (1.5%)

Peptic ulcer disease	230 (3.1%)	215 (2.9%)
Tobacco use, no. (%)		
Current smoker	696 (9.2%)	686 (9.1%)
Missing	404 (5.4%)	569 (7.6%)
Medications at the time of randomization, no. (%)		
Aspirin use before study		
Missing	404 (5.4%)	569 (7.6%)
No	286 (3.8%)	280 (3.7%)
Yes	6850 (90.8%)	6687 (88.7%)
81 mg	5823/6850 (85.0%)	5724/6687 (85.6%)
162 mg	168/6850 (2.5%)	142/6687 (2.1%)
325 mg	845/6850 (12.3%)	812/6687 (12.1%)
Clopidogrel	1448 (20.7%)	1401 (20.5%)
Prasugrel	108 (1.5%)	95 (1.4%)
Other antiplatelet medication (Ticlopidine, Vorapaxar, Cilostazol)	27 (0.3%)	28 (0.4%)

A total of 15039/15076 participants (99.8%) had available medical history via electronic health record data.
Age, sex, race, ethnicity, tobacco use, and medication use prior to randomization were reported by the participants.

Table S6. Treatment effect on participant-reported quality of life over time

	81 mg		325 mg	
	N	**Mean Score (SE)**	**N**	**Mean Score (SE)**
Describe current health*				
Randomization	7540	3.27 (0.010)	7536	3.25 (0.010)
Month 6	5980	3.26 (0.009)	5677	3.24 (0.010)
Year 1	5346	3.25 (0.010)	5059	3.23 (0.010)
Month 18	4264	3.24 (0.010)	4054	3.22 (0.010)
Year 2	3039	3.23 (0.011)	2860	3.20 (0.011)
Able to run errands and shop*				
Randomization	7540	4.46 (0.010)	7536	4.47 (0.010)
Month 6	5977	4.43 (0.009)	5667	4.44 (0.009)
Year 1	5339	4.40 (0.010)	5056	4.40 (0.010)
Month 18	4262	4.38 (0.010)	4050	4.37 (0.010)
Year 2	3040	4.35 (0.011)	2859	4.34 (0.012)
In the past 7 days, I felt depressed**				
Randomization	7540	1.66 (0.010)	7536	1.67 (0.010)
Month 6	5975	1.67 (0.009)	5669	1.68 (0.009)
Year 1	5339	1.68 (0.009)	5059	1.69 (0.009)
Month 18	4255	1.68 (0.009)	4053	1.70 (0.010)
Year 2	3037	1.69 (0.010)	2857	1.70 (0.011)
In the past 7 days, I felt fatigued**				
Randomization	7540	2.23 (0.011)	7536	2.23 (0.011)
Month 6	5975	2.23 (0.010)	5672	2.24 (0.010)
Year 1	5338	2.24 (0.010)	5053	2.25 (0.010)
Month 18	4260	2.25 (0.011)	4050	2.26 (0.011)
Year 2	3037	2.25 (0.012)	2861	2.27 (0.012)

In the past 7 days, I had problems with sleep**				
Randomization	7540	2.05 (0.011)	7536	2.07 (0.011)
Month 6	5972	2.05 (0.010)	5669	2.08 (0.010)
Year 1	5334	2.06 (0.010)	5055	2.09 (0.010)
Month 18	4258	2.06 (0.011)	4049	2.10 (0.011)
Year 2	3038	2.06 (0.012)	2858	2.10 (0.012)
Trouble doing regular activities*				
Randomization	7540	4.19 (0.010)	7536	4.20 (0.010)
Month 6	5977	4.19 (0.010)	5674	4.18 (0.010)
Year 1	5337	4.18 (0.010)	5054	4.16 (0.010)
Month 18	4263	4.17 (0.010)	4043	4.14 (0.011)
Year 2	3037	4.16 (0.012)	2858	4.12 (0.012)
In the past 7 days, pain interfered with normal activities**				
Randomization	7540	2.00 (0.012)	7536	2.02 (0.012)
Month 6	5980	2.01 (0.011)	5676	2.04 (0.011)
Year 1	5344	2.03 (0.011)	5060	2.06 (0.011)
Month 18	4263	2.04 (0.011)	4054	2.08 (0.012)
Year 2	3039	2.06 (0.013)	2862	2.10 (0.013)

Responses are scored on a Likert scale from 1 to 5., with 5 indicating the best health.

* Higher scores are better.

** Lower scores are better.

Table S7. Primary effectiveness end point based on secondary randomization group (3 months vs. 6 months of follow-up)

	81 mg N (Rate)[1]	325 mg N (Rate)[1]	Hazard ratio 81 mg vs 325 mg (95% CI)
Follow-up interval			
3 months	279 (6.8%)	297 (7.8%)	0.92 (0.78 - 1.08)
6 months	311 (7.7%)	272 (7.2%)	1.13 (0.96 - 1.33)

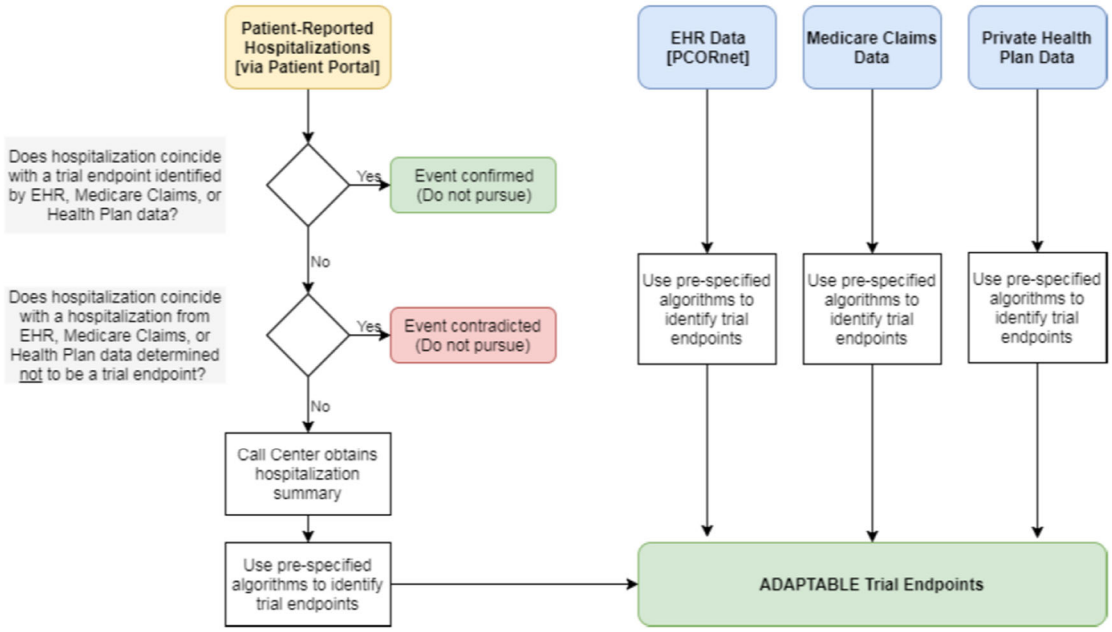
CI, confidence interval.
Rates are calculated at median follow-up (26.2 months) using the Kalbfleisch & Prentice cumulative incidence function estimator. Events include data from electronic health record data, CMS claims, private insurance claims and confirmed participant reported outcomes (PROs). The hazard ratios (HR) reflect comparisons between 81mg with 325mg, such hat HR >1 indicate higher event rates in the 81mg group.

Table S8. Sensitivity analyses to assess impact of prior aspirin dose, non-adherence, COVID-19, and under-reporting of events and misclassification of events on the primary effectiveness end point

Outcome	81 mg N (Rate)	325 mg N (Rate)	HR (95% CI) 81mg mg vs 325mg mg
Impact of prior aspirin dose -- Landmark Analysis at 10 Days*			
Death/MI/Stroke	583 (7.3%)	560 (7.5%)	1.02 (0.91 - 1.15)
Impact of COVID-19			
Death/MI/Stroke	462 (7.5%)	457 (7.6%)	1.00 (0.88 – 1.14)
Impact of non-adherence†			
Death/MI/Stroke	673 (3.6 events per 100 patient-years)	321 (2.9 events per 100 patient-years)	1.25 (1.10 - 1.43)
Impact of Under-Reporting of Events			
Death/MI/Stroke	590 (7.6%)	569 (7.9%)	1.02 (0.91 - 1.14)
Impact of Misclassification of Events*			
Death/MI/Stroke Primary Diagnosis Position Only	533 (6.6%)	517 (6.8%)	1.01 (0.90 – 1.14)
All Diagnosis Positions	650 (8.1%)	629 (8.4%)	1.01 (0.91 – 1.13)

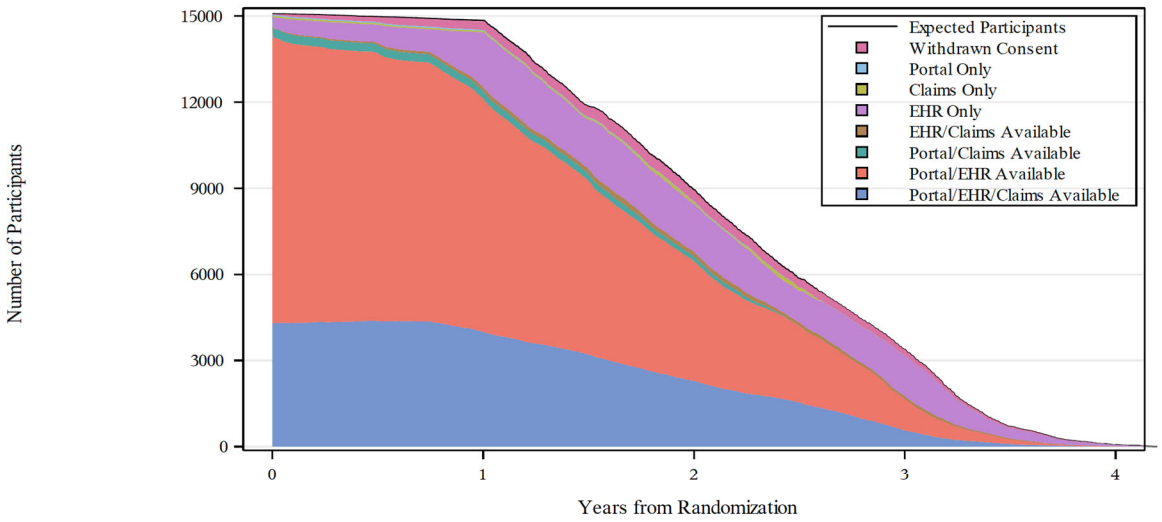
Events include data from electronic health record data, CMS claims, private insurance claims and confirmed participant reported outcomes (PROs). The hazard ratios (HR) reflect comparisons between 81mg with 325mg, such hat HR >1 indicate higher event rates in the 81mg group.
*Rates are calculated at median follow-up (26.2 months) using the Kalbfleisch & Prentice cumulative incidence function estimator.
†Rates and HR reflect the effect of the time-varying reported dose on the primary effectiveness end point. Rates are calculated as annualized event rates (events per 100 patient-years).

Figure S1. End point ascertainment and confirmation for non-fatal events



End points were identified through electronic sources (including EHR data, CMS claims or private insurance claims data) or patient reported via the patient portal. When participants reported events via the patient portal or Call Center, the initial step was to match those events with data from electronic sources. If the event was confirmed as a study end point, the patient-reported event was not pursued further. If the patient-reported event was also identified via electronic data sources but was not confirmed as a study end point (eg, the hospitalization did not qualify as an end point), the patient-reported event was not pursued further. If the patient-reported event was not identified via electronic data sources, then the Call Center was activated to contact the patient, obtain authorization for release of medical records, and then contact the health system where medical care occurred. A review of the hospital billing codes was then performed to confirm or refute the non-fatal end point. Some clinical end points required medical record review if billing codes were not available or unclear.

Figure S2. Participant data availability over trial follow-up

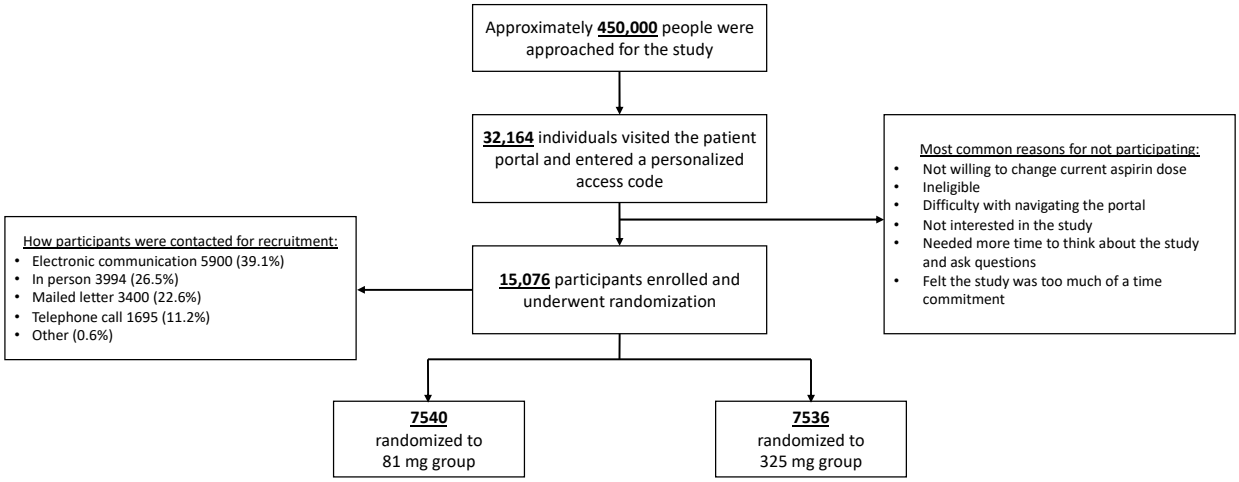


Portal/EHR/Claims Available	4315	3994	2286	572	0
Portal/EHR Available	10337	8140	4185	1114	2
Portal/Claims Available	365	276	170	0	0
EHR/Claims Available	0	130	149	90	8
EHR Only	0	1886	1657	1408	49
Claims Only	0	54	77	0	0
Portal Only	50	31	23	6	0
Withdrawn Consent	9	301	370	197	1

Six hundred eighty-three participants enrolled in CMS after randomization, and 116 participants enrolled in private insurance after randomization. Sixty-seven participants were missing a start date for private insurance enrollment. Randomization date was used as a surrogate. Fourteen CMS participants had a break in coverage for a median of 62 days. Sixteen health plan participants had a break in coverage for a median of 366 days.

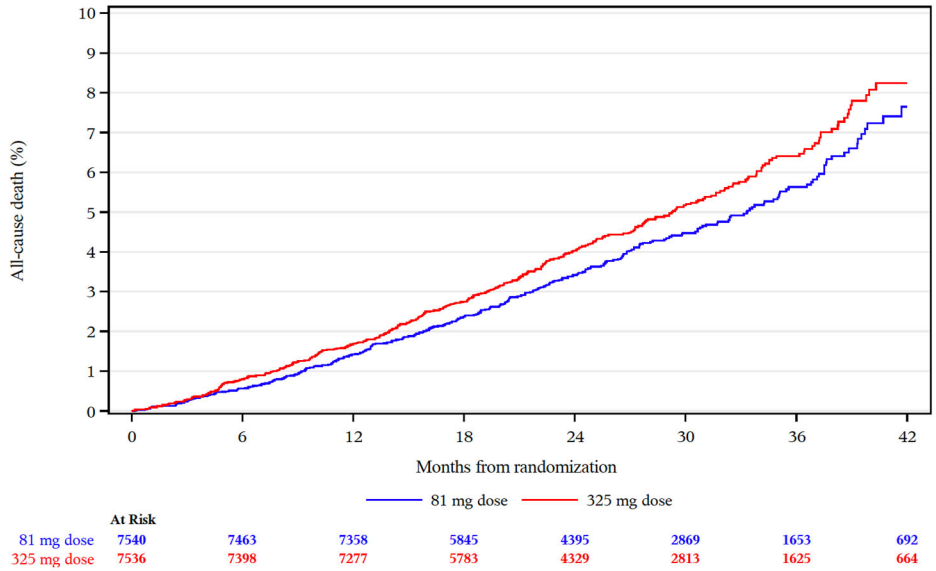
The height of the figure corresponds to the expected number of participants at a given time since randomization. Drop-off after Year 1 reflects staggered enrollment and censoring at June 30, 2020.

Figure S3. Randomization, treatment, and follow-up of participants



Top reasons participants visited the portal but did not enroll included: Not willing to change their current aspirin dose; ineligible; difficulty with navigating the portal; not interested in the study; needed more time to think about the study and ask questions; and felt the study was too much of a time commitment.
For participants who withdrew consent from the trial, all information up to the point of withdrawal was included in the analyses. Vital status was ascertained after trial closure via multiple methods including electronic health record review, telephone calls from the Call Center, and internet searches.

Figure S4. Time-to-event curves for all-cause mortality

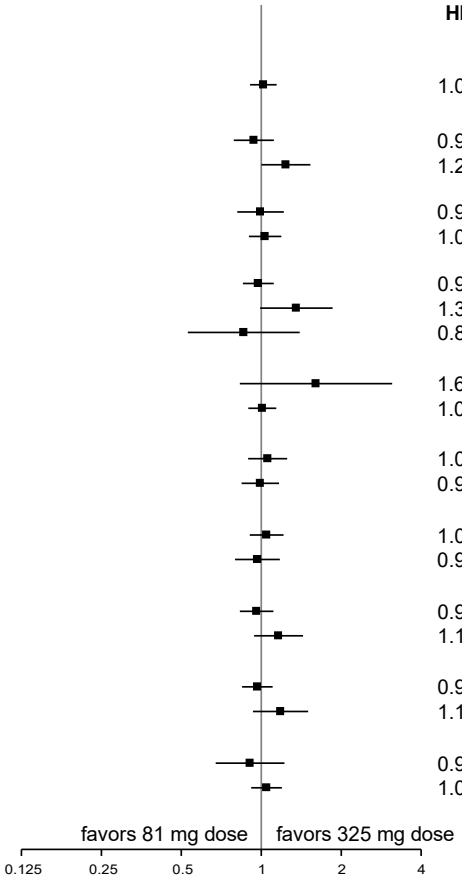


Cumulative incidence of all-cause mortality reported in each treatment group.

Figure S5. Analyses of heterogeneity of treatment effect for the primary effectiveness outcome

Primary Efficacy Subgroup Analysis for Protocol Defined Death/MI/Stroke by Randomized Treatment Groups
Participant Self-Reported, EHR and Claims Data

	81 mg dose N (Rate)*	325 mg dose N (Rate)*	HR† (95% CI)
Overall	590 (7.28%)	569 (7.51%)	1.02 (0.91 - 1.14)
Age‡			
>= 65 yrs	364 (7.12%)	378 (7.96%)	0.94 (0.79 - 1.12)
< 65 yrs	226 (7.54%)	191 (6.80%)	1.24 (1.00 - 1.53)
Sex			
Female	186 (7.79%)	193 (8.43%)	0.99 (0.81 - 1.21)
Male	404 (7.06%)	376 (7.08%)	1.03 (0.90 - 1.19)
Race			
White	432 (6.70%)	433 (7.12%)	0.97 (0.85 - 1.11)
Black	91 (12.27%)	68 (10.69%)	1.36 (0.99 - 1.86)
Other	33 (6.88%)	33 (7.69%)	0.86 (0.53 - 1.39)
Ethnicity			
Hispanic	24 (7.67%)	14 (5.94%)	1.61 (0.83 - 3.11)
Not Hispanic	530 (7.26%)	513 (7.44%)	1.01 (0.89 - 1.14)
Diabetes			
No	283 (5.97%)	258 (5.82%)	1.06 (0.89 - 1.25)
Yes	288 (9.28%)	295 (9.99%)	0.99 (0.84 - 1.17)
Chronic kidney disease			
No	370 (5.82%)	347 (5.65%)	1.05 (0.90 - 1.21)
Yes	201 (13.73%)	206 (15.68%)	0.97 (0.80 - 1.18)
P2Y12 inhibitor use			
No	359 (5.87%)	361 (6.64%)	0.96 (0.83 - 1.11)
Yes	188 (11.49%)	161 (10.08%)	1.16 (0.94 - 1.44)
Study visit method			
Internet	439 (6.28%)	449 (6.70%)	0.97 (0.85 - 1.10)
Non-Internet	151 (13.73%)	120 (12.96%)	1.18 (0.93 - 1.50)
Weight§			
< 70 kg	81 (10.50%)	95 (12.22%)	0.91 (0.67 - 1.22)
>= 70 kg	451 (7.09%)	419 (7.10%)	1.05 (0.92 - 1.20)



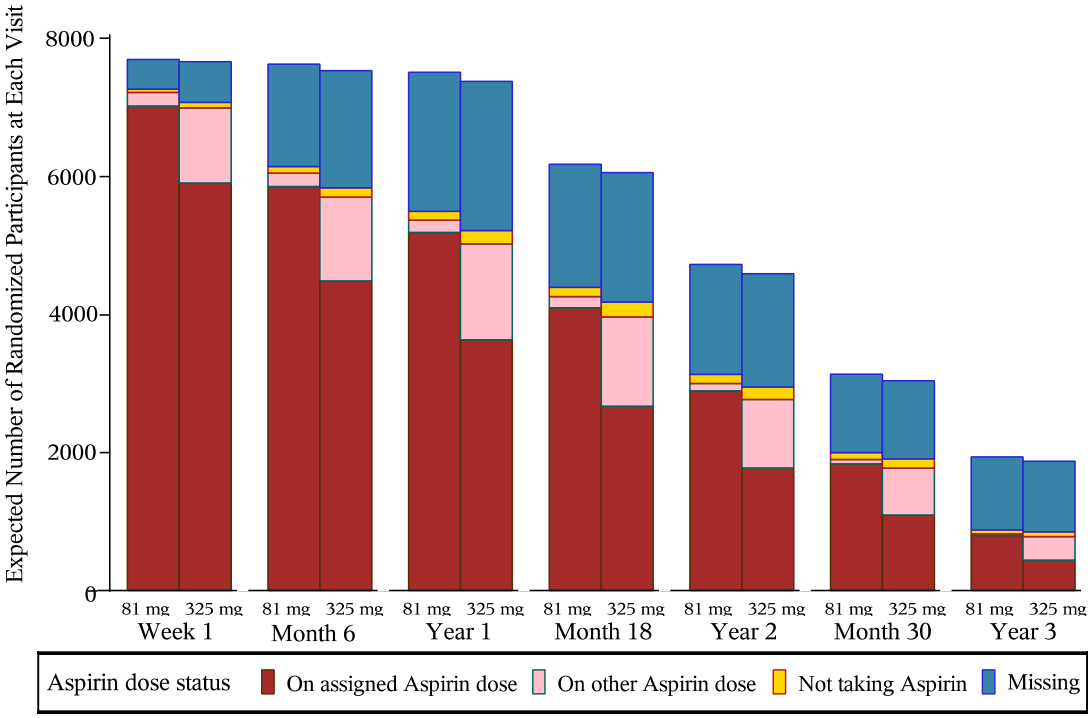
* N represents the total number of events over follow-up. Rates are calculated at median follow-up (26.2 months) using the Kalbfleisch & Prentice CIF estimator. Events include data from EHR, CMS claims, private insurance claims and confirmed participant reported outcomes (PROs).

†Hazard ratios are obtained from a Cox proportional hazards model fit with randomized aspirin dose, subgroup and the dose by subgroup interaction. Hazard ratios compare 81 mg to 325 mg within each subgroup level. The interaction p-value is derived using the Wald chi-square statistic.

‡Age was non-linearly associated with the primary endpoint, and was modeled using restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentiles. The hazard ratio comparing 81 mg to 325 mg is presented for age=60 (age < 65) and age=70 (age >= 65).

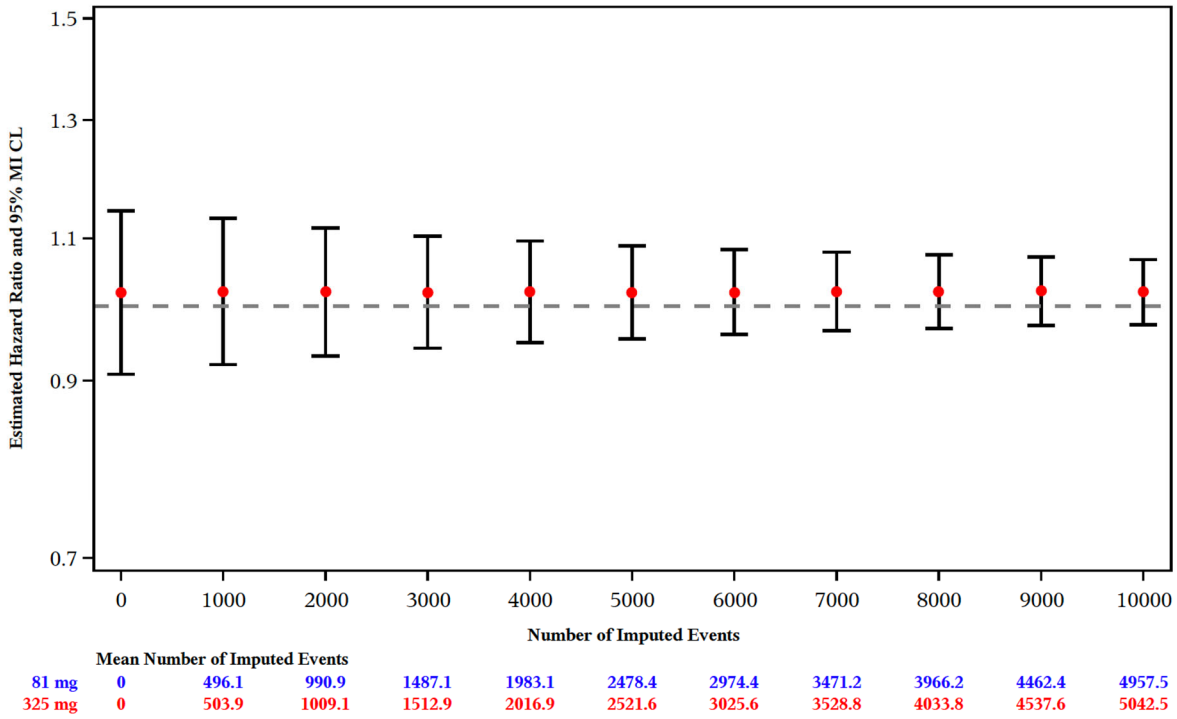
§Analysis of this subgroup was not pre-specified.

Figure S6. Adherence to randomized study dose over time



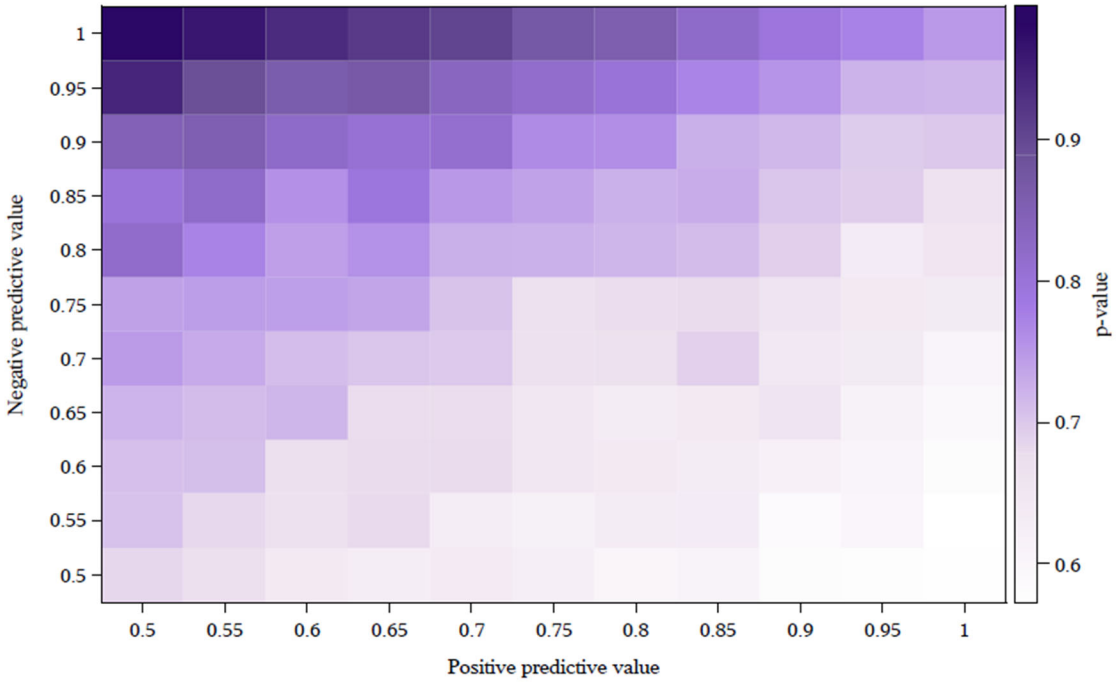
Study medication adherence was ascertained at every visit to the patient portal or via the Call Center. Red represents those participants that were adherent to the randomized study dose. Pink represents those participants that were taking a different dose than the randomized study dose. Yellow represents those participants that were not taking aspirin at the time of the encounter. Blue represents those participants with missing dose information at each visit.

Figure S7. Sensitivity analysis to assess impact of under-reporting of events on primary efficacy analysis



The results of the tipping point analysis to assess impact of under-reporting of events on the primary efficacy analysis are reported as HRs (red dots, 81 mg vs 325 mg) and corresponding 95% confidence intervals (error bars). The HR and CI with Number of Imputed Events = 0 corresponds to the primary efficacy analysis. Events were added (and imputed 1000 times) in increments of 1000 until the number of participants at risk of under-reporting was reached. This analysis assumes that under-reporting was non-differential between randomized aspirin dose groups (i.e. the impact of under-reporting is loss of power, not bias), so the HR point estimate was consistently very close to 1.0 as in the primary result. Imputed event times beyond the participant's censoring time were censored and not imputed; the Mean Number of Imputed Events reflects those event times that were included in the sensitivity analysis.
The confidence interval limits never crossed the significance threshold.

Figure S8. Sensitivity analysis to assess impact of misclassification of events on primary efficacy analysis



The results of the tiping point analysis to assess impact of misclassification of events on the primary efficacy analysis are reported as p-values represented in this heat map. Positive predictive value (PPV) and negative predictive value (NPV) were varied from 0.5 to 1 to reclassify primary efficacy endpoints for those participants at risk of misclassification as defined by available endpoint data. The p-values were generated from a test of the randomized treatment effect based on a Cox model as specified for the primary analysis. The p-value corresponding to PPV=1 and NPV=1 corresponds to the primary efficacy analysis. The point PPV=1 and NPV=.5 represents the greatest number of events in analysis (half of non-events are reclassified to events and no events are reclassified to non-events). The point PPV=.5 and NPV=1 represents the smallest number of events in analysis (no non-events are reclassified to events and half of events are reclassified to non-events).
No combination of PPV and NPV in the 0.5 to 1.0 range yielded a change in the results of primary analysis.