



Development of a standardized definition for clinically significant bleeding in the ASPirin in Reducing Events in the Elderly (ASPREE) trial



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ABSTRACT

Background: Bleeding is the major risk of aspirin treatment, especially in the elderly. A consensus definition for clinically significant bleeding (CSB) in aspirin primary prevention trials is lacking in the literature.

Methods: This paper details the development, modification, application, and quality control of a definition for clinically significant bleeding in the ASPirin in Reducing Events in the Elderly (ASPREE) trial, a primary prevention trial of aspirin in 19,114 community-dwelling elderly men and women. In ASPREE a confirmed bleeding event needed to meet criteria both for substantiated bleeding and clinical significance. Substantiated bleeding was defined as: 1) observed bleeding, 2) a reasonable report of symptoms of bleeding, 3) medical, nursing or paramedical report, or 4) imaging evidence. Bleeding was defined as clinically significant if it: 1) required transfusion of red blood cells, 2) required admission to the hospital for > 24 h, or prolonged a hospitalization, with bleeding as the principal reason, 3) required surgery to stop the bleeding, or 4) resulted in death. Bleeding sites were subclassified as upper gastrointestinal, lower gastrointestinal, intracranial (hemorrhagic stroke, subarachnoid hemorrhage, subdural hematoma, extradural hematoma, or other), or other sites. Potential events were retrieved from medical records, self-report or notification from treating doctors. Two reviewers adjudicated each event using electronic adjudication software, and discordant cases were reviewed by a third reviewer. Adjudication rules evolved to become more strictly defined as the trial progressed and decision rules were added to assist with frequent scenarios such as post-operative bleeding.

Conclusions: This paper provides a detailed methodologic description of the development of a standardized definition for clinically significant bleeding and provides a benchmark for development of a consensus definition for future aspirin primary prevention trials.

Trial registration: ASPREE is registered on the International Standard Randomized Controlled Trial Number Register (ISRCTN83772183) and on clinicaltrials.gov (NCT01038583).

1. Background

Aspirin has long been recommended to prevent recurrent events in patients of all ages with established cardiovascular disease because of its favorable benefit to risk ratio in this population [1,2]. Evidence is also building for use of aspirin in primary prevention of cardiovascular disease and cancer, but the balance of risk of bleeding and benefit of

disease prevention is much more closely matched [3–5]. Meta-analyses of primary prevention trials and a large cohort studies found a 50–60% increased risk for major gastrointestinal or extracranial bleeding with low-dose aspirin, with age as the strongest risk factor [5–8].

The ASPirin in Reducing Events in the Elderly (ASPREE) trial is a primary prevention trial examining the benefits and risks of daily aspirin 100 mg or placebo in 19,114 US and Australian adults aged 70

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Table 1
Definitions of bleeding from aspirin primary prevention trials.

Study	Definition of Bleeding	Dosing of Aspirin	Characteristics of study participants
BDS, 1988 [14]	<ul style="list-style-type: none"> ● Hemorrhagic stroke (fatal, non-fatal) ● Fatal gastric hemorrhage ● Fatal peptic ulcer ● Non-fatal bleed, not cerebral ● Non-fatal peptic ulcer 	500 mg/day (or 300mg enteric coated tablet if later requested)	<ul style="list-style-type: none"> ● Male physicians
PHS I, 1989 [15]	<ul style="list-style-type: none"> ● Death from gastrointestinal (GI) hemorrhage ● Bleeding events requiring transfusion ● Other (easy bruising, hematemesis, melena, nonspecific gastrointestinal bleeding, epistaxis, or other bleeding) 	325mg every other day	<ul style="list-style-type: none"> ● Male physicians ● 40–84 years old
ETDRS, 1992 [16]	<ul style="list-style-type: none"> ● Hemoglobin < 100 g/L or hematocrit < 0.30 ● Hematuria ● Blood in stool 	325 mg/day	<ul style="list-style-type: none"> ● Age 18-70 ● Diabetes mellitus, with diabetic retinopathy
HOT, 1998 [17]	<p>Reporting method not stated, no indication of severity</p> <ul style="list-style-type: none"> ● Fatal bleeding (GI, cerebral, other) ● Non-fatal major bleeding, defined as life threatening, disabling, or requiring hospital admission (GI, cerebral, nasal, other) ● Minor bleeding (GI, nasal, purpura, other) 	75 mg/day	<ul style="list-style-type: none"> ● Age 50-80 ● Hypertensive ● Diastolic BP 100–115 mm Hg
TPT, 1998 [18]	<ul style="list-style-type: none"> ● Hemorrhagic stroke (fatal, non-fatal) ● Subarachnoid hemorrhage (fatal, non-fatal) ● GI bleeding (Upper, lower, indeterminate) ● Other bleeding <p>Major bleeding: confirmed cerebral hemorrhages and fatal or life-threatening hemorrhages at other sites that required transfusion and/or surgery. Intermediate bleeding episodes: Bleeding not meeting major definition, eg, macroscopic hematuria, larger bruises, prolonged nose bleeds. Minor bleeding episodes: bruising, nose bleeds, rectal bleeding, pink or red urine</p>	75 mg/day	<ul style="list-style-type: none"> ● Men ● Age 45-69 ● High risk of heart disease
PPP, 2001 [19]	<ul style="list-style-type: none"> ● Hemorrhagic stroke ● Other intracranial bleeding ● “Severe” GI bleeding ● “Severe” ocular bleeding, epistaxis, other bleeding <p>No definition of severe</p>	100 mg/day	<ul style="list-style-type: none"> ● Age 50 and older ● High cardiovascular risk
WHS, 2005 [20]	<ul style="list-style-type: none"> ● Hemorrhagic stroke ● GI bleeding (fatal or non-fatal, requiring transfusion) ● Peptic ulcer ● Hematuria ● Easy bruising ● Epistaxis 	100mg every other day	<ul style="list-style-type: none"> ● Women ● 45 and older
JPAD, 2008 [21]	<ul style="list-style-type: none"> ● Hemorrhagic stroke (fatal, or non-fatal) ● GI hemorrhage ● Other hemorrhage ● Non-bleeding GI event ● Anemia <p>Severe GI hemorrhage defined as requiring transfusion</p>	81 or 100 mg/day	<ul style="list-style-type: none"> ● Age 30-85 ● Type 2 diabetes ● No history of vascular disease
POPADAD, 2008 [22]	<p>GI bleeding – no indication of severity</p>	100 mg/day	<ul style="list-style-type: none"> ● Age 40 and older ● Type 1 or 2 diabetes ● Ankle-brachial index < 0.99 ● No symptomatic vascular disease
AAA, 2010 [23]	<ul style="list-style-type: none"> ● Hemorrhagic stroke (fatal or non-fatal) ● Subarachnoid/subdural hemorrhage (fatal or non-fatal) ● GI hemorrhage ● Other hemorrhage ● Gastrointestinal ulcer ● Retinal hemorrhage ● Severe anemia (not defined) <p>Major GI and other hemorrhage defined as requiring admission to hospital to control bleeding. Admission only to investigate bleeding was not included.</p>	100 mg/day	<ul style="list-style-type: none"> ● Age 50-75 ● No history of vascular disease ● Ankle-brachial index < 0.95
JPPP, 2014 [24]	<ul style="list-style-type: none"> ● Serious extracranial hemorrhage requiring transfusion or hospitalization ● gastrointestinal hemorrhage; gastroduodenal ulcer; reflux esophagitis; erosive gastritis; stomach 	100 mg/day	<ul style="list-style-type: none"> ● Age 60-85 ● Cardiovascular risk factors

years and older (65 years and older for US minorities) [9]. The primary outcome is ‘disability-free survival’, with primary endpoints comprising all-cause mortality, incident dementia, or persistent physical disability. The composite outcome was chosen to allow an overall assessment of the benefit of aspirin, and differs from previous primary prevention trials which generally have focused on cardiovascular outcomes. The primary safety endpoint is major hemorrhagic events. Hemorrhagic stroke and non-stroke clinically significant bleeding (CSB) are included within this composite outcome. CSB includes non-stroke intracranial bleeding and extracranial bleeding.

While a consensus definition for bleeding in cardiovascular trials has been proposed [10], no similar attempt has occurred for in trials of aspirin for primary prevention. Previous primary prevention trials have varied in the sites and severity of bleeding that were reported, the definition of severe or major bleeding, and whether anemia or a specific hemoglobin level was included (Table 1). During the initial stages of developing a definition of CSB for the ASPREE protocol, operational definitions from published primary and secondary prevention trials, as well as interventional cardiovascular trials, were consulted. These definitions were revisited by the co-chairs of the Endpoint Adjudication

Committee in planning how to operationalize the ASPREE CSB endpoint as defined in the protocol. They decided that a focus on bleeding that was fatal or required transfusion, hospitalization, or surgery was in keeping with the trial's overall emphasis on major functional outcomes. Less serious bleeding episodes or isolated changes in laboratory values were therefore not included.

As adjudication proceeded, the ASPREE investigators further refined the CSB definition and aimed to establish adjudication rules that could be applied consistently over time and between different adjudicators, and could potentially be adopted for use in future primary prevention trials. In this paper, we describe the methods for ascertaining possible bleeding episodes, the development of a standardized definition of CSB, and methods to achieve consensus through the use of “decision rules”. We use illustrative cases that highlight issues commonly encountered during adjudication.

2. Methods

2.1. ASPREE study design and participants

The study design and baseline participant characteristics are described elsewhere [9,11]. Briefly, ASPREE is a double-blind, randomized trial comparing oral enteric-coated acetyl salicylic acid 100 mg or matching placebo. Participants age 70 years and older (65 and older for U.S. minorities) were recruited from Australian general practice and

U.S. community settings. They were free of dementia, physical disability, cardiovascular disease, and other conditions contraindicating the use of aspirin or requiring its use. All participants were screened for anemia, and were excluded if their hemoglobin level was < 12 g/dl in men or < 11 g/dl in women. People taking aspirin without a clear indication were able to participate if they and their physician agreed to discontinue aspirin. ASPREE has multiple Institutional Review Board approvals in the U.S. and Australia.

Recruitment ended in December 2014 with 16,703 Australian and 2411 U.S. participants. The median age of participants at randomization was 74 (range 65–98) years and 56% were women. Approximately 55% of the U.S. cohort were from minority groups. Following enrollment, participants were seen for annual visits and contacted by telephone at the 6-month mark following each visit.

2.2. ASPREE CSB event collection and adjudication process

A structured questionnaire was administered to participants at 6 month phone calls and annual visits for the purpose of detecting events that may be primary or secondary endpoints, including CSB events. With regard to bleeding events, participants were asked “In the past 6 months, or since we last saw or spoke with you, has your doctor diagnosed or treated you for clinically significant bleeding requiring hospitalization?” Affirmative responses were followed by queries about the name of the hospital and date of admission. Participants and family

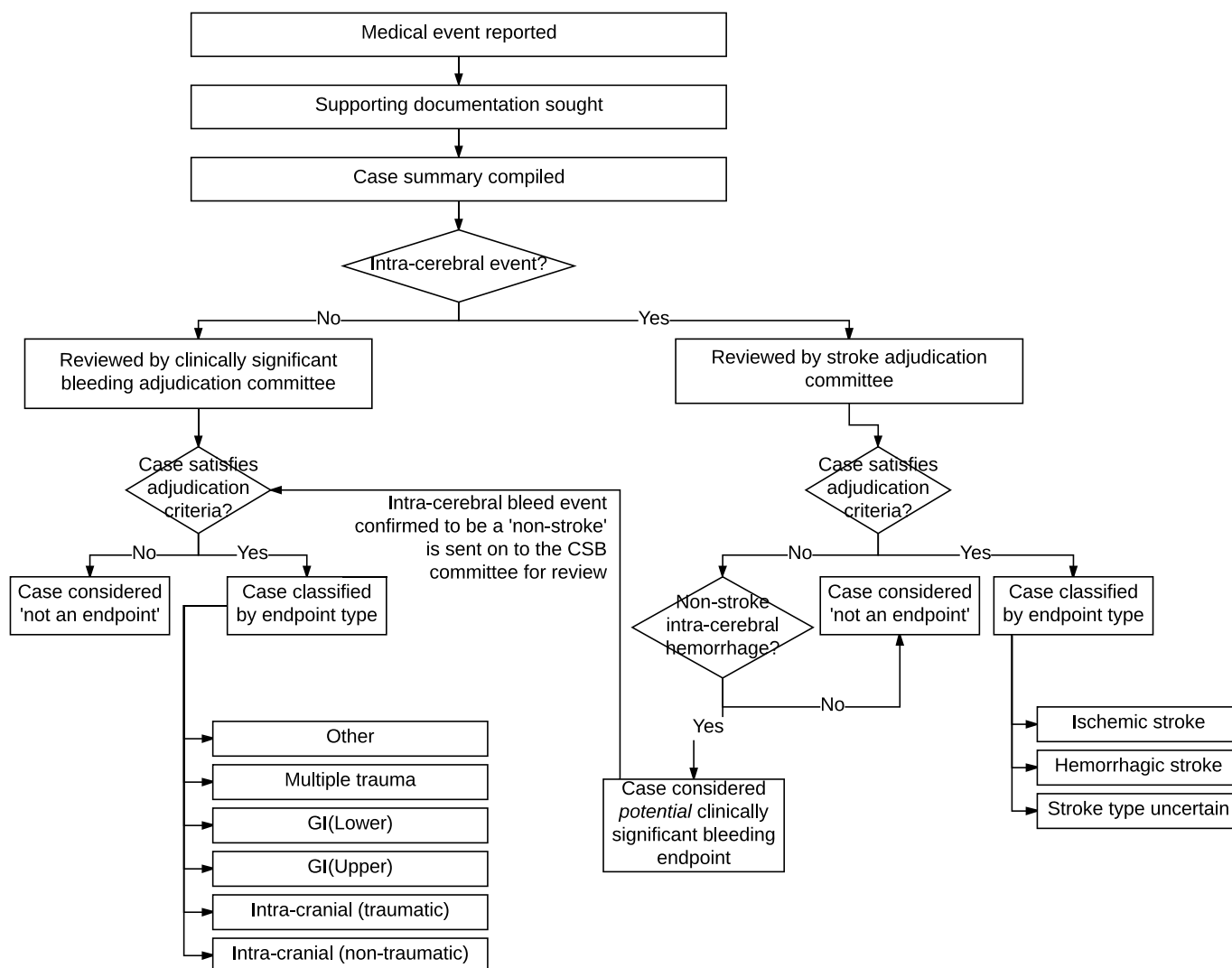


Fig. 1. ASPREE Adjudication Process Chart.

members may have also reported bleeding events at any time by contacting study staff. In addition, medical records from all overnight hospitalizations and deaths were screened for possible bleeding events. Following detection of any potential endpoint, supporting documentation for events was sought from hospitals, specialists, and general practitioners or primary care providers (Fig. 1).

A case summary was compiled for each event by trained staff at the Australian National Coordinating Centre. The first page of the case summary included a description of the key information points from the available supporting documents. Case summaries were reviewed by an experienced medical practitioner and then assigned electronically to two adjudicators for review who were presented with the case summary and asked to provide an adjudication outcome. For CSB events, one of the adjudicators also entered data for event sub-classification. Bleeding sites were sub-classified as upper gastrointestinal, lower gastrointestinal, intracranial, multiple trauma, or other sites. Intracranial bleeding was further sub-classified as traumatic or non-traumatic. Discordant case were reviewed by a third adjudicator who provided a final adjudication outcome and sub-classification. CSB adjudicators were also able to mark difficult cases for discussion on teleconference calls.

Between 2010 and 2016 intracerebral bleeds were reviewed by the stroke adjudication committee and intracranial extracerebral bleeds such as extradural, subdural and subarachnoid hemorrhage, were reviewed by the CSB adjudication committee. This process was changed in late 2016 at the request of the ASPREE Data Safety and Monitoring Board. Starting in 2017, cases of subarachnoid hemorrhage and cases where the site of intracranial bleeding was unclear were seen first by the stroke adjudication committee. This change was made to better align with the extensive neurological expertise on the stroke adjudication committee. It also streamlined the adjudication process, since subarachnoid extension of intracerebral hemorrhage then only required adjudication by one committee. Events adjudicated to be non-stroke intracranial bleeds were then sent for further assessment by the CSB committee. Non-stroke intracranial bleeds were sub-classified by anatomical location (subdural, extradural, other.)

2.3. Adjudicator web portal

Adjudication of primary and secondary endpoints was facilitated by the adjudication module of the ASPREE Web Accessible Database. Upon logging in to the module, adjudicators were only able to access cases

assigned to them and were blinded to the decision of the other adjudicator. Following entry of adjudication outcome by the second adjudicator, the program detected if the results were discordant, and if so the case automatically appeared on the list of pending adjudications for the third adjudicator.

2.4. Protocol and initial development of clinically significant bleeding definition

At the commencement of the study, the ASPREE protocol defined clinically significant bleeding as non-stroke intracranial bleeding and extracranial bleeding that was fatal or required transfusion, hospitalization, or surgery. To test the definition, the co-chairs of the Endpoint Adjudication Committee independently adjudicated 67 events between 2011 and 2013 and then discussed discordance and cases that fell outside the protocol definition but were considered to be significant bleeding events. As a result of these discussions “transfusion” was defined as intravascular transfusion of red blood cells; “hospitalization” was defined as admission to the hospital for > 24 h, or prolongation of a hospitalization with bleeding as the principal reason; and “surgery” was defined as any surgical procedure required to stop the bleeding, excluding endoscopic procedures and colonoscopies (Table 2). Fatal hemorrhage was defined as death due to a bleeding event.

In addition to meeting the clinically significant definition above, in ASPREE a confirmed CSB event needs to meet the criteria for substantiated bleeding (Table 2). Decision rules were developed to support the protocol definitions as follows: “substantiated bleeding” was defined as: 1) observed bleeding, including through endoscopic instruments, 2) a reasonable report of symptoms of bleeding (e.g. melena or hematemesis), 3) medical, nursing or paramedical report, or 4) imaging evidence such as a computed tomography or magnetic resonance report. Low hemoglobin level, a drop in hemoglobin level, or a positive fecal occult blood test alone did not satisfy the criterion of substantiated bleeding.

Following confirmation of the protocol definition and supporting decision rules, a committee with expertise in internal medicine, hematology, and gastroenterology was convened. In 2016, a neurologist consultant was included in the CSB adjudication committee to assist with difficult cases of intracranial bleeding. Quarterly conference calls were held to discuss difficult cases and discordant adjudications, leading to further refinements described below.

Table 2

Criteria for substantiation and clinical significance of bleeding events in the ASPREE trial, and decision rules. Bleeding events were required to meet both criteria before being recorded as clinically significant. Decision rules were applied for relevant cases to ensure consistency over time and between adjudicators.

CRITERIA FOR SUBSTANTIATED BLEEDING		
A	Observed bleeding	e.g. bleeding observed at cystoscopy
B	Reasonable report of bleeding symptom	e.g. description of melena
C	Medical, nursing or paramedical report	e.g. emergency notes
D	Imaging evidence	e.g. CT brain showing hemorrhage
CRITERIA FOR CLINICALLY SIGNIFICANT BLEEDING		
A	Bleeding necessitating red cell transfusion	
B	Bleeding requiring hospital admission for > 24 h	
C	Bleeding requiring surgery for hemostasis	Excluding endoscopic procedures
D	Bleeding resulting in death	
DECISION RULES		
1	If hospitalisation criterion is to be utilised, bleeding must be the principal reason for hospitalisation, prolongation of hospitalisation or surgery and must be substantiated.	
2	A positive fecal occult blood test, anemia, or haemoglobin drop is insufficient to substantiate bleeding.	
3	Additional adjudication will occur on whether intracranial bleeding was spontaneous (non-traumatic) or induced (traumatic).	
4	Elective inpatient surgical procedure (includes therapeutic endoscopic procedures) with prolonged stay, repeat surgery, or transfusion: Does not meet criteria	
5	Elective inpatient surgical (includes therapeutic endoscopic procedures) readmitted after discharge primarily for bleeding: Does meet criteria	
6	Elective outpatient procedure (includes therapeutic endoscopic procedures) admitted primarily for bleeding: Does meet criteria	
7	Non-elective inpatient procedure (includes therapeutic endoscopic procedures) readmitted, prolonged stay, repeat surgery, or transfused: Does meet criteria	

2.5. Development of additional clinically significant bleeding decision rules

During the trial the CSB committee found it necessary to develop decision rules related to elective surgery because of the frequency of elective procedures and peri-operative bleeding in this age group. The study protocol states that participants will be advised to contact the research staff or research clinic when any surgery is planned. In general, cessation of study medication was managed by the treating physician. If queried about how study medication should be managed prior to surgery, ASPREE trial staff advised physicians to treat the patient as if they were taking aspirin and to tell the patient accordingly whether to temporarily cease the study medication.

The CSB committee reasoned that bleeding rates should thus be similar in the aspirin and placebo groups for elective procedures, but might not be similar for non-elective procedures where study medication cannot be stopped in advance. Furthermore, because bleeding is common and expected for many procedures, it was difficult for adjudicators to determine what constituted excess bleeding above an expected threshold. To reduce over-reporting of bleeding and misclassification, bleeding following elective inpatient surgery or endoscopic procedures was not counted as CSB, even if the bleeding was severe, required prolongation of the hospital stay, required transfusion, or required re-operation to stop the bleeding. For patients who were discharged from the hospital and later readmitted for bleeding, or were admitted due to bleeding following elective outpatient surgery or therapeutic endoscopic procedures, the event was adjudicated as a CSB event. Bleeding following non-elective hospitalized surgery (such as for hip fractures or emergency coronary bypass surgery) was also classified as a CSB event if it prolonged the hospital stay, or required transfusion, another operation to stop the bleeding, or re-admission. After several rounds of case discussion the CSB committee found these rules for post-surgical bleeding reduced the number of discordant cases and were generally straightforward to apply.

We describe cases that illustrate how the ASPREE CSB definition and decision rules were applied.

- 1) *Anemia without overt bleeding*: The participant was admitted to the hospital with iron deficiency anemia, epigastric discomfort, and weight loss, and had recently received an iron and blood transfusion as an outpatient. During the admission, upper gastrointestinal endoscopy showed multiple gastric and duodenal erosions but no active bleeding. Colonoscopy also did not reveal any bleeding source. Proton pump inhibitors were prescribed. This case was not considered to be a CSB event because there was no record of overt bleeding, and therefore did not meet criteria of substantiated bleeding. The participant was hospitalized several months later with hematemesis and that case was adjudicated as a CSB event.
- 2) *Bleeding not the principal reason for admission to hospital or death*: The participant was in a head-on automobile crash and was admitted to the hospital with facial fractures, pneumocephalus, sternal fracture, bilateral pulmonary contusions, and multiple rib fractures. A subarachnoid hemorrhage and a subdural hematoma were treated conservatively. The participant died 24 days later following a complicated course that included pneumonia. At post-mortem examination the immediate cause of death was judged to be large volume aspiration and the underlying cause of death was multiple injuries sustained in a motor vehicle accident. This case was judged not to be a CSB event because the intracranial bleeding was not the principal reason for the hospital admission or the death and the bleeding was not treated surgically.
- 3) *Bleeding not the principal reason for admission to hospital or death*: The participant had several episodes of hematuria that led to an outpatient evaluation. A renal ultrasound scan showed multifocal bladder tumors likely to be transitional cell carcinoma. He was admitted for elective transurethral resection of the bladder tumor. Several bladder tumors were resected. Free clot was observed in the

bladder and continuous irrigation was instituted post-operatively. The patient was discharged after a successful test of void on post-operative day 2. Although the patient had hematuria and blood clots were observed in the bladder, the case was adjudicated as not a CSB event because the principal reason for the hospital admission was to resect the bladder tumors rather than to treat the bleeding. (Similar cases in women involve hospitalizations for elective uterine surgery to diagnose or treat suspected malignancy after outpatient evaluations for vaginal bleeding.)

- 4) *Management of bleeding as an outpatient*: The participant fell and struck his head. A week later an outpatient CT scan showed a subdural hematoma that appeared chronic rather than acute. The participant was advised to return in 4–6 weeks for a repeat scan or sooner if he had more symptoms; the repeat scan showed resolution. This case was judged not to be a CSB event because the patient was not admitted or treated surgically.
- 5) *Elective surgical procedures with bleeding complications*: The participant had an elective lumbar laminectomy and later during the same hospital stay required surgery to drain a lumbar epidural hematoma. This case was adjudicated as not a CSB event because the laminectomy was elective, even though the hospital stay was prolonged and surgery was required to treat post-operative bleeding.
- 6) *Emergency procedure with documented bleeding*: The participant fell and sustained a hip fracture requiring emergency surgery and transfusion of 2 units of red blood cells for intraoperative bleeding with a post-operative hemoglobin drop from 11.6 to 6.3 g/dl. This case was adjudicated as a CSB event as the patient had intraoperative and postoperative blood loss and the procedure was non-elective.
- 7) *Post-operative bleeding requiring re-admission*: The participant underwent elective knee replacement surgery and was discharged, but re-admitted four days later for severe bleeding at the surgical site that required re-operation and drain placement. Although the knee replacement was elective, this case was adjudicated as a CSB event since the bleeding required re-admission.
- 8) *Outpatient procedure that required hospital admission for bleeding*: The participant had a rectal polyp removed as an outpatient. Following the procedure there was rectal bleeding with a hemoglobin drop to 7.3 g/dl. The participant was admitted to the hospital for observation and transfusion. Although the polypectomy was elective, the case was adjudicated as a CSB event since the patient required admission and transfusion.
- 9) *Death due to bleeding*: The participant unexpectedly developed throat discomfort, rapidly lost consciousness, and could not be resuscitated. Post-mortem examination showed hemopericardium and dissection of the thoracic aorta that was judged to be the cause of death. This case was adjudicated as a CSB event since there was substantiated fatal bleeding.
- 10) *Non-stroke intracranial bleeding*: The participant had several separate events of left hand weakness and paresthesia and an episode of left-sided facial droop and expressive dysphasia. All episodes lasted only minutes and resolved completely. The participant was admitted to the hospital where a brain CT scan revealed blood in the central sulcus and thickening of the right pre- and post-central gyri. An MRI revealed hemorrhage in the central sulcus with superficial ischemia in the pre- and post-central gyri, which were felt to be explained best by amyloid angiopathy. The case was reviewed by the stroke committee and felt not to be a stroke, and was referred to the CSB committee, which adjudicated it as a CSB event.

As the process of refining the decision rules occurred for much of the adjudication period of ASPREE, a decision was taken, with approval by the ASPREE Principal Investigators, to conduct an audit and review of all cases at the end of the ASPREE study. This quality control audit used the full complement of decision rules to ensure the ASPREE clinically

significant bleeding criteria were applied systematically across all cases over the 7 year period of the study. The audit was conducted by two members of the committee, two independent clinicians and the clinical Chair of the Endpoint Adjudication Committee. A future publication will include quantitative information about the number of case reports, positive and negative confirmation rates, discordance rates, and quality control audit results.

3. Discussion

The purpose of capturing and adjudicating CSB events in ASPREE is to understand the risk of aspirin treatment for primary prevention in the elderly, specifically bleeding events that are important enough to require surgery, transfusion or hospitalization, or to result in death. A definition of CSB was established that would make clear which clinical categories of bleeding were included and which were not. In most previous aspirin primary prevention trials to date, the working definition of clinically significant bleeding is not readily available in the published literature and often needs to be inferred from tables and footnotes. Given the absence of clear guidance, the CSB committee developed decision rules over the course of ASPREE to deal with new types of bleeding cases as they arose, with features outside the protocol definitions, to ensure that similar cases in the future would be adjudicated systematically in accord with the decision rule. Holding regular adjudicator teleconferences to discuss difficult and discordant cases was an essential tool for developing consensus about bleeding events that occurred in a wide variety of circumstances and organ systems.

A consensus bleeding definition has been proposed to address the heterogeneity in bleeding definitions used in cardiovascular trials in acute coronary syndromes and percutaneous coronary interventions [10]. This definition describes five levels of bleeding from none to fatal, focuses heavily on procedural bleeding, and incorporates both clinical events and changes in hemoglobin levels. Other cardiovascular trial bleeding definitions include Thrombolysis in Myocardial Infarction (TIMI), International Society on Thrombosis and Hemostasis (ISTH), and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial criteria [12]. All three of these have subclassifications of bleeding severity, and the TIMI and ISTH major bleeding definitions include change in hemoglobin levels. Similarly, the definition of major bleeding in the definition proposed for trials of antihemostatic agents (anticoagulants, antiplatelet drugs, and fibrinolytic agents) includes a change in hemoglobin level [13]. These trials regularly measure hemoglobin peri-procedurally, particularly with significant interventions. None of these definitions was well-suited for a primary prevention trial in which there is no procedural intervention likely to precipitate bleeding and study hemoglobin measures are conducted annually.

Previous primary prevention studies have widely variable definitions of what constitutes significant bleeding (Table 1) [14–24]. For example, the Hypertension Optimal Treatment (HOT) trial reported major bleeding from gastrointestinal, cerebral and other sites that was fatal, life-threatening, disabling, or required hospital admission, but did not include transfusion as an indicator of severity [17]. In contrast, the Aspirin for Asymptomatic Atherosclerosis (AAA) trial included as major bleeds only those that required hospital admission to control the bleeding, but not admissions for diagnostic purposes or observation [23]. The Japanese Primary Prevention of Atherosclerosis with Aspirin in Diabetes (JPAD) reported bleeding from gastrointestinal and other sites, but did not report the level of severity of bleeding other than to state that 4 episodes of severe gastrointestinal bleeding required transfusion in the aspirin group [21]. Only a few studies reported on anemia (not defined further in AAA or JPAD) or low hemoglobin levels (Early Treatment of Diabetic Retinopathy Study [ETDRS]) [16,21,23]. This lack of consensus prompted the ASPREE investigators to develop their own criteria that would represent clinical and patient-important

outcomes related to bleeding. In addition, the difficulty of determining from the medical literature clear definitions of terms or the methods for adjudicating bleeding events prompted the development of this report.

There are a number of limitations to the ASPREE definition of CSB. First, we cannot be certain we have captured all important aspirin-related bleeding, as some bleeding may result in a subclinical blood loss where overt bleeding does not occur and a source is never localized. However, hemoglobin is measured annually as a safety laboratory measure in ASPREE; thus differential changes in hemoglobin and the development of anemia will be reported separately from CSB. Second, while our decision rules regarding elective surgical procedures were developed to improve consistency and concordance of adjudication, they may have resulted in misclassification of some serious bleeding events that could have been related to aspirin. Third, we did not include patients in developing the CSB definition, and in future work, it will be important to consider including bleeding events of significance to patients' quality of life that may not have been captured in our criteria. Examples of bleeding that patients may consider important are presentation to the emergency department for epistaxis management and subdural hematomas that are managed in the outpatient setting. Finally, whether this definition is broadly generalizable in other populations and healthcare settings is unknown. The strengths of our approach include independent adjudication of all CSB endpoints by at least two reviewers and ongoing refinement of criteria and decision rules that adjudicators find easier to apply with consistency.

4. Conclusion

This paper presents a detailed description of the development, adaptation, and application of a definition of clinically significant bleeding in a large primary prevention trial of aspirin in community-dwelling elderly men and women. To our knowledge no other trial has presented similarly detailed methods, which are needed given the importance of bleeding risk in this population. This detailed methodologic description of the adjudication process and definition of bleeding events will aid in the interpretation of the ASPREE trial results. It provides a benchmark for development of a consensus definition for future aspirin primary prevention trials.

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