Contemporary Clinical Trials Communications 11 (2018) 30–36

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

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

Karen L. Margolis[a,*], Suzanne E. Mahady[b], Mark R. Nelson[c], Diane G. Ives[d], Suzanne Satterfield[e,1], Carlene Britt[b], Saifuddin Ekram[b], Jessica Lockery[b], Erin C. Schwartz[a], Robyn L. Woods[b], John J. McNeil[b], Erica M. Wood[b]

[a] HealthPartners Institute, Mailstop 23301A, PO Box 1524, Minneapolis, MN, 55440-1524, USA
[b] School of Public Health & Preventive Medicine, Monash University, Melbourne, Australia
[c] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
[d] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
[e] University of Tennessee Health Science Center, Memphis, TN, USA

ARTICLE INFO

Keywords:
Aspirin
Primary prevention
Methods
Hemorrhage
Bleeding

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

* Corresponding author.
E-mail addresses: Karen.L.Margolis@HealthPartners.com (K.L. Margolis), suzanne.mahady@monash.edu (S.E. Mahady), mark.nelson@utas.edu.au (M.R. Nelson), dianives@pitt.edu (D.G. Ives), carlene.britt@monash.edu (C. Britt), saifuddin.ekram@monash.edu (S. Ekram), jessica.lockery@monash.edu (J. Lockery), Erin.C.Schwartz@HealthPartners.com (E.C. Schwartz), robyn.woods@monash.edu (R.L. Woods), john.mcneil@monash.edu (J.J. McNeil), erica.wood@monash.edu (E.M. Wood).
[1] Deceased.

https://doi.org/10.1016/j.conctc.2018.05.015
Received 19 January 2018; Received in revised form 16 May 2018; Accepted 21 May 2018
Available online 22 May 2018

Table 1
Definitions of bleeding from aspirin primary prevention trials.

Study	Definition of Bleeding	Dosing of Aspirin	Characteristics of study participants
BDS, 1988 [14]	• 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)	• Male physicians
PHS I, 1989 [15]	• 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	• Male physicians • 40–84 years old
ETDRS, 1992 [16]	• Hemoglobin < 100 g/L or hematocrit < 0.30 • Hematuria • Blood in stool Reporting method not stated, no indication of severity	325 mg/day	• Age 18-70 • Diabetes mellitus, with diabetic retinopathy
HOT, 1998 [17]	• 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	• Age 50-80 • Hypertensive • Diastolic BP 100–115 mm Hg
TPT, 1998 [18]	• Hemorrhagic stroke (fatal, non-fatal) • Subarachnoid hemorrhage (fatal, non-fatal) • GI bleeding (Upper, lower, indeterminate) • Other bleeding 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	75 mg/day	• Men • Age 45-69 • High risk of heart disease
PPP, 2001 [19]	• Hemorrhagic stroke • Other intracranial bleeding • “Severe” GI bleeding • “Severe” ocular bleeding, epistaxis, other bleeding No definition of severe	100 mg/day	• Age 50 and older • High cardiovascular risk
WHS, 2005 [20]	• Hemorrhagic stroke • GI bleeding (fatal or non-fatal, requiring transfusion) • Peptic ulcer • Hematuria • Easy bruising • Epistaxis	100mg every other day	• Women • 45 and older
JPAD, 2008 [21]	• Hemorrhagic stroke (fatal, or non-fatal) • GI hemorrhage • Other hemorrhage • Non-bleeding GI event • Anemia Severe GI hemorrhage defined as requiring transfusion	81 or 100 mg/day	• Age 30-85 • Type 2 diabetes • No history of vascular disease
POPADAD, 2008 [22]	GI bleeding – no indication of severity	100 mg/day	• Age 40 and older • Type 1 or 2 diabetes • Ankle-brachial index < 0.99 • No symptomatic vascular disease
AAA, 2010 [23]	• 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) Major GI and other hemorrhage defined as requiring admission to hospital to control bleeding. Admission only to investigate bleeding was not included.	100 mg/day	• Age 50-75 • No history of vascular disease • Ankle-brachial index < 0.95
JPPP, 2014 [24]	• Serious extracranial hemorrhage requiring transfusion or hospitalization • gastrointestinal hemorrhage; gastroduodenal ulcer; reflux esophagitis; erosive gastritis; stomach	100 mg/day	• 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