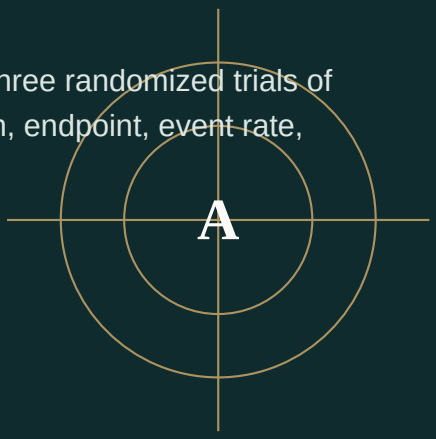
MEDICAL EVIDENCE MAP SPECIMEN

When similar trials answer different questions.

A source linked comparison of ARRIVE, ASCEND, and ASPREE: three randomized trials of daily low dose aspirin for primary prevention, mapped by population, endpoint, event rate, bleeding evidence, and current source status.



REAL SPECIMEN PUBLIC RECORD ONLY NO CLIENT INVOLVED

This evidence map demonstrates research structure. It is not a systematic review, a clinical guideline, or medical advice. It does not tell any person whether to start, continue, or stop aspirin.

MEDICAL EVIDENCE MAP 01 SCOPE

The defined question

The same intervention can produce different evidence when the enrolled population, outcome definition, and follow up differ.

Field	Defined project
Question	How did the populations, outcome definitions, observed event rates, and bleeding findings differ across ARRIVE, ASCEND, and ASPREE?
Audience	A physician, investigator, research lead, or policy reader who needs a rapid but auditable orientation before deeper review.
Record	The three primary trial reports, trial registrations, a later ASPREE follow up report, and current US preventive guidance for context.
Output	An evidence map, trial profiles, outcome crosswalk, benefit and harm comparison, currency note, limits register, and linked source ledger.
Source standard	Primary trial reports and official registries first. Guidance is kept separate from trial evidence.
Boundary	No individual recommendation, pooled estimate, guideline synthesis, or claim of systematic completeness.

WHY THIS RECORD

All three trials tested 100 mg daily aspirin against placebo in primary prevention settings and appeared in 2018. That surface similarity makes them a useful test of whether a researcher preserves the differences that govern interpretation.

The governing caution

> A trial result belongs first to the population enrolled, the endpoint defined, and the period observed. It cannot be moved intact into a different clinical question.

MEDICAL EVIDENCE MAP 02 ANSWER

Executive map

The three reports do not provide three repetitions of the same answer.

Trial	Population	Cardiovascular finding	Bleeding finding	Interpretive constraint
ARRIVE	Adults selected for moderate estimated risk; diabetes excluded	Primary endpoint 4.29% with aspirin and 4.48% with placebo; HR 0.96	Gastrointestinal bleeding 0.97% and 0.46%; HR 2.11	Observed event rate was much lower than expected; authors said the intended moderate risk question could not be addressed
ASCEND	Adults with diabetes and no evident cardiovascular disease	Serious vascular events 8.5% and 9.6%; rate ratio 0.88	Major bleeding 4.1% and 3.2%; rate ratio 1.29	Absolute vascular benefit was largely counterbalanced by bleeding hazard
ASPREE	Community dwelling older adults without cardiovascular disease, dementia, or disability	Cardiovascular disease 10.7 and 11.3 per 1000 person years; HR 0.95	Major hemorrhage 8.6 and 6.2 per 1000 person years; HR 1.38	Cardiovascular disease was a prespecified secondary endpoint, not the primary endpoint

What survives comparison

Across the three trials, aspirin did not produce a uniform net answer. ASCEND reported fewer serious vascular events and more major bleeding. ARRIVE did not resolve its intended moderate risk question because the observed event rate was lower than expected. ASPREE found no significantly lower cardiovascular disease rate and a higher major hemorrhage rate in healthy older adults.

DO NOT POOL BY EYE

The outcome definitions and reporting scales differ. Percentages over trial follow up cannot be directly compared with events per 1000 person years as though they were the same measure.

MEDICAL EVIDENCE MAP 03 APPLICABILITY

Population is part of the result

The label primary prevention conceals material differences in baseline risk and eligibility.

Field	ARRIVE	ASCEND	ASPREE
Defining population	Men 55 or older and women 60 or older with risk factors intended to indicate moderate cardiovascular risk	Adults with diabetes and no evident cardiovascular disease	Community dwelling adults 70 or older, or 65 or older for Black and Hispanic US participants
Key exclusions stated in report	Diabetes and high bleeding risk	Evident cardiovascular disease	Cardiovascular disease, dementia, or disability
Randomized	12,546	15,480	19,114
Setting	501 sites in seven countries	United Kingdom	Australia and United States
Follow up	Median 60 months	Mean 7.4 years	Median 4.7 years
Immediate use limit	Not a clean estimate for the intended moderate risk population after unexpectedly low event accrual	Not a trial of adults without diabetes	Not a trial of younger adults or adults with established cardiovascular disease

Applicability question

Before a result is cited, the working record should state whether the target population resembles the trial population in age, cardiovascular history, diabetes status, bleeding risk, and contemporary preventive treatment.

ABSENCE RECORDED

These papers do not answer the use of aspirin for secondary prevention, during anticoagulant therapy, or for an individual with a specific bleeding history. Those are different questions.

The endpoints do not line up

A shared subject does not create a shared endpoint.

Trial	Primary efficacy endpoint	Bleeding endpoint used here	What must not be inferred
ARRIVE	First cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack	Gastrointestinal bleeding events, mostly mild	This bleeding measure is not equivalent to ASCEND major bleeding or ASPREE major hemorrhage
ASCEND	First serious vascular event: myocardial infarction, stroke or transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage	Major bleeding: intracranial, sight threatening ocular, gastrointestinal, or other serious bleeding	Its composite is not identical to ARRIVE or ASPREE cardiovascular disease
ASPREE	Primary trial endpoint was disability free survival: death, dementia, or persistent physical disability	Major hemorrhage: hemorrhagic stroke, symptomatic intracranial bleeding, or serious extracranial bleeding	Cardiovascular disease and major hemorrhage were prespecified secondary endpoints

Why the crosswalk changes the reading

A composite can move because of one component while others remain unchanged. A broader composite can collect more events than a narrower one. A safety outcome that counts mostly mild gastrointestinal bleeds cannot be treated as the same object as a major hemorrhage endpoint requiring hospitalization, transfusion, surgery, or death.

CONTROL APPLIED

Outcome names are retained exactly enough to preserve their content. The map does not replace them with the generic labels benefit and harm.

MEDICAL EVIDENCE MAP 05 TRIAL PROFILE

ARRIVE

The intended moderate risk study enrolled a population whose observed event rate was much lower than expected.

Element	Record
Design	Randomized, double blind, placebo controlled, multicenter trial in seven countries
Intervention	Enteric coated aspirin 100 mg once daily versus placebo
Participants	12,546 randomized; diabetes and high bleeding risk excluded
Primary result	269 of 6,270 participants in the aspirin group, 4.29%, and 281 of 6,276 in the placebo group, 4.48%; HR 0.96, 95% CI 0.81 to 1.13; p=0.6038
Bleeding result	Gastrointestinal bleeding in 61 participants, 0.97%, and 29, 0.46%; HR 2.11, 95% CI 1.36 to 3.28; p=0.0007; events were mostly mild
Author interpretation	The event rate was much lower than expected. The authors said the role of aspirin in the intended moderate risk population could therefore not be addressed
Funding	Bayer

The failure mode avoided

A superficial summary says aspirin did not work in moderate risk adults. The paper supports a narrower statement: the intention to treat comparison was not statistically significant, but unexpectedly low event accrual meant the intended moderate risk question was not resolved.

Primary source: Gaziano JM et al. Lancet. 2018;392:1036 to 1046. DOI 10.1016/S0140-6736(18)31924-X. Trial registration NCT00501059.

MEDICAL EVIDENCE MAP 06 TRIAL PROFILE

ASCEND

The diabetes trial makes the benefit and bleeding tradeoff visible in the same population and follow up period.

Element	Record
Design	Randomized placebo controlled trial with a factorial omega 3 comparison
Intervention	Aspirin 100 mg daily versus matching placebo
Participants	15,480 adults with diabetes and no evident cardiovascular disease
Follow up	Mean 7.4 years
Efficacy result	Serious vascular events in 658 participants, 8.5%, and 743, 9.6%; rate ratio 0.88, 95% CI 0.79 to 0.97; p=0.01
Safety result	Major bleeding in 314 participants, 4.1%, and 245, 3.2%; rate ratio 1.29, 95% CI 1.09 to 1.52; p=0.003
Author interpretation	The absolute benefits were largely counterbalanced by the bleeding hazard

Absolute view

Over the reported follow up, the between group difference was 1.1 percentage points for serious vascular events and 0.9 percentage points for major bleeding. Those simple differences are descriptive, not adjusted effect estimates, but they show why a relative risk alone is an incomplete briefing measure.

CONTROL APPLIED

Benefit and harm remain paired. The map does not report the vascular reduction without the major bleeding increase.

Primary source: ASCEND Study Collaborative Group. N Engl J Med. 2018;379:1529 to 1539. DOI 10.1056/NEJMoa1804988. Registrations ISRCTN60635500 and NCT00135226.

MEDICAL EVIDENCE MAP 07 TRIAL PROFILE

ASPREE

The older adult trial used disability free survival as its primary endpoint and reported cardiovascular disease as a secondary endpoint.

Element	Record
Design	Randomized placebo controlled trial in Australia and the United States
Intervention	Enteric coated aspirin 100 mg daily versus placebo
Participants	19,114 community dwelling older adults without cardiovascular disease, dementia, or disability
Follow up	Median 4.7 years
Endpoint status	Cardiovascular disease and major hemorrhage were prespecified secondary endpoints; the primary endpoint was disability free survival
Cardiovascular result	10.7 events per 1000 person years with aspirin and 11.3 with placebo; HR 0.95, 95% CI 0.83 to 1.08
Hemorrhage result	8.6 events per 1000 person years and 6.2; HR 1.38, 95% CI 1.18 to 1.62; p<0.001

The hierarchy matters

The cardiovascular and hemorrhage paper reports important prespecified outcomes, but it is not accurate to call cardiovascular disease the primary endpoint of ASPREE. Endpoint status belongs in the evidence map because it governs how a result is described.

Primary source: McNeil JJ et al. N Engl J Med. 2018;379:1509 to 1518. DOI 10.1056/NEJMoa1805819. Trial registration NCT01038583.

What the numbers permit

The comparison preserves denominators, reporting scale, uncertainty, and outcome definition.

Result	Aspirin	Placebo	Relative estimate	Permitted reading
ARRIVE primary endpoint	269/6,270, 4.29%	281/6,276, 4.48%	HR 0.96, 95% CI 0.81 to 1.13	No statistically significant difference; intended moderate risk question unresolved
ARRIVE gastrointestinal bleeding	61/6,270, 0.97%	29/6,276, 0.46%	HR 2.11, 95% CI 1.36 to 3.28	Higher gastrointestinal bleeding; mostly mild
ASCEND serious vascular events	658, 8.5%	743, 9.6%	Rate ratio 0.88, 95% CI 0.79 to 0.97	Lower serious vascular event incidence
ASCEND major bleeding	314, 4.1%	245, 3.2%	Rate ratio 1.29, 95% CI 1.09 to 1.52	Higher major bleeding incidence
ASPREE cardiovascular disease	10.7 per 1000 person years	11.3 per 1000 person years	HR 0.95, 95% CI 0.83 to 1.08	No significantly lower cardiovascular disease rate
ASPREE major hemorrhage	8.6 per 1000 person years	6.2 per 1000 person years	HR 1.38, 95% CI 1.18 to 1.62	Higher major hemorrhage rate

NO FALSE PRECISION

The map does not calculate a pooled treatment effect. A defensible meta analysis would require a protocol, comprehensive search, eligibility rules, risk of bias assessment, outcome harmonization, and a stated statistical model.

Unit rule

Retain the measure used by the source. A hazard ratio, rate ratio, cumulative percentage, and event rate per person time each answer a different quantitative question.

Six controls applied

A polished summary can still be wrong. These controls make the weaknesses visible before the work is used.

Failure mode	Control in this evidence map	Visible result
Authority mistaken for support	Each proposition is matched to the trial report or registry that actually supports it	Source ledger and proposition matrix
Currency assumed	A 2025 ASPREE follow up and current preventive guidance were checked separately from the 2018 trials	Currency note
Conflict silently resolved	Differing populations, endpoints, and scales are preserved rather than flattened	Population and endpoint crosswalks
Absence unrecorded	Questions outside the selected record are named	Limits register
Provenance broken	Stable identifiers, DOI, PMID, and registry numbers are retained	Linked source ledger
Limits unstated	The document states that it is not systematic, not guidance, and not individual advice	Boundary on cover and close

What a reviewer can check

A reader can open the primary report, locate the population, endpoint, denominator, effect estimate, confidence interval, and author interpretation, then compare each to the corresponding field in this document.

CONFIDENCE STATEMENT

High confidence in the reported trial characteristics and results because they are taken from primary reports. Lower confidence in transfer to any unstudied population because that is an applicability judgment beyond this specimen.

Currency changes the record, not the past result

Later evidence belongs in a separate layer so it informs the reader without rewriting the randomized trial.

Later source	What it adds	What it does not do
ASPREE extended follow up, 2025	Across in trial and post trial observation, no long term MACE benefit was observed; HR 1.04, 95% CI 0.94 to 1.15. Major hemorrhage remained higher; HR 1.24, 95% CI 1.10 to 1.39	It does not turn the post trial period into a continued randomized treatment comparison; exposure changed after the trial
USPSTF recommendation, 2022	For adults 40 to 59 with at least 10% ten year CVD risk, initiation is an individual decision with small net benefit. The USPSTF recommends against initiating at age 60 or older	Guidance is not a trial result and does not replace individualized clinical judgment
Trial registries	Stable identifiers, protocol fields, recruitment status, and posted updates	A registry entry does not replace the peer reviewed report for the reported outcome

Separation rule

> The 2018 randomized findings remain the 2018 randomized findings. Later follow up and later guidance are linked as subsequent layers with their own design, date, and authority.

Sources were checked for this specimen on 1 September 2026.

Limits register

The map records what was not searched, not compared, or not decided.

- This is a bounded evidence map, not a systematic review of aspirin for primary prevention.
- The search was designed to verify three named trials and selected subsequent context, not to identify every eligible study.
- No formal risk of bias assessment tool was applied.
- No pooled estimate, network comparison, subgroup analysis, or certainty grade was produced.
- The cardiovascular composites and bleeding outcomes were not harmonized across trials.
- The map does not address secondary prevention, pregnancy, perioperative use, anticoagulant combinations, cancer prevention, or an individual patient's risk profile.
- The 2025 ASPREE extension includes an observational post trial period and must not be described as uninterrupted randomized treatment exposure.
- No recommendation is made for starting, continuing, or stopping aspirin.

What would be required for reliance

A clinical, policy, or publication decision would require a question specific protocol, comprehensive current search, full text eligibility review, risk of bias assessment, appropriate synthesis, specialist review, and patient or population context.

MEDICAL BOUNDARY

Atlas organizes public medical evidence. It does not diagnose, treat, prescribe, or replace a licensed clinician, statistician, systematic reviewer, or subject matter specialist.

Linked source ledger

Every major field can be traced to a primary report or official public record.

ID	Source	Use	Status
M01	ARRIVE primary report, Lancet 2018, PMID 30158069, DOI 10.1016/S0140-6736(18)31924-X	Design, population, endpoint, results, interpretation, funding	Primary trial report
M02	ARRIVE registry, NCT00501059	Stable trial identity and registration record	Official registry
M03	ASCEND primary report, NEJM 2018, PMID 30146931, DOI 10.1056/NEJMoa1804988	Design, population, efficacy and safety results, interpretation	Primary trial report
M04	ASCEND registry, NCT00135226	Stable trial identity and registration record	Official registry
M05	ASPREE cardiovascular and bleeding report, NEJM 2018, PMID 30221597, DOI 10.1056/NEJMoa1805819	Population, endpoint hierarchy, cardiovascular and hemorrhage results	Primary trial report
M06	ASPREE registry, NCT01038583	Stable trial identity and registration record	Official registry
M07	ASPREE extended follow up, Eur Heart J 2025, PMID 40796244	Long term and post trial currency layer	Later peer reviewed report
M08	USPSTF recommendation, 2022	Current US preventive guidance context	Official guidance

Provenance rule

PubMed records provide stable bibliographic identifiers and abstracts. Trial registrations preserve trial identity and protocol fields. The full report remains the source for detailed methods, tables, adjudication, subgroup analysis, and limitations.

MEDICAL EVIDENCE MAP 13 CLOSE

What this specimen demonstrates

The deliverable is designed so that a knowledgeable reader can challenge it without first rebuilding it.

Control	Delivered evidence
Question defined	One bounded comparison stated before collection
Population preserved	Eligibility differences retained beside every trial
Endpoint hierarchy preserved	Primary and secondary outcomes not silently exchanged
Numbers made auditable	Denominators, scales, relative estimates, confidence intervals, and follow up retained
Conflict explained	Different findings interpreted through population, endpoint, and event accrual
Currency checked	Later evidence and guidance added as separate layers
Limits stated	The record says what it cannot support
Provenance retained	DOI, PMID, registration, and live links carried into the final form

Professional boundary

This document is a public medical evidence map specimen. It was not commissioned by a client, contains no confidential information, and is not medical advice. It should not be relied upon for diagnosis, treatment, prescribing, or an individual decision about aspirin.

ATLAS CONCORDAT

Atlas accepts a question, an unfinished body of work, or a difficult record and returns an analysis built for expert review. Every material proposition is tied to its source. Every limit is stated. The judgments remain visible.

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