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Effect of aspirin on deaths associated with sepsis in healthy older people (ANTISEPSIS): a randomised, double-blind, placebo-controlled primary prevention trial

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Summary

Background—Sepsis is a serious global health issue and a major cause of death and disability. The availability of a simple, community-based preventive strategy could substantially reduce the burden of sepsis. We aimed to establish whether low-dose aspirin reduced deaths or hospital admissions associated with sepsis in older people.

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Contributors

DPE and ESM initiated the study, wrote the funding submission, managed the chief investigators' (DPE, ESM, KL, RLW, JEL, RW) activities, adjudicated study events, did the study analyses, and wrote the manuscript. KL contributed to the funding submission, adjudicated study events, and contributed to the manuscript. RLW initiated and designed the ASPREE study, oversaw its conduct and shared responsibility for its data, contributed to the ANTISEPSIS funding submission, and contributed to the manuscript. JEL was the data manager for ASPREE, designed and managed the ANTISEPSIS endpoint adjudication system, managed its chief investigators' activities, and contributed to the manuscript. SLM and DP adjudicated study events and contributed to the manuscript. RW contributed to the funding submission, data analysis oversight, management of study data, and contributed to the manuscript. EMM and AS collected study event material and contributed to the manuscript. JJM, MRN, and CMR initiated and designed the ASPREE study, oversaw its conduct and shared responsibility for its data, and contributed to the ANTISEPSIS manuscript. All authors approved the manuscript in its final form.

Declaration of interests

MRN reports personal fees from Bayer AG. All other authors declare no competing interests.

Data sharing

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) will be available on publication of this article. Meta-data and data dictionaries will be available on application. Requests for data access will be via the ASPREE principal investigators and the ANTISEPSIS principal investigator with details for applications provided through the website. The data will be made available to investigators whose proposed use to achieve the specified aims has been approved by a review committee identified for this purpose. Approved data will be accessed through a web-based data portal safe haven, based at Monash University, Australia.

See **Online** for appendix

For **applications** see https://www.ASPREE.org

Methods—ANTISEPSIS was a substudy of ASPREE (a randomised controlled primary prevention trial of low-dose aspirin [100 mg per day] compared with placebo in community dwelling older adults conducted in Australia and the USA), with the Australian cohort included in the ANTISEPSIS substudy. Inclusion criteria were participants aged at least 70 years who did not have major illnesses. Participants were block randomised (1:1) via a centralised web portal and stratified by general practice and age. Participants, investigators, and staff were masked to the intervention. Teams of clinical specialist investigators assessed potential sepsis events to establish if they satisfied the primary endpoint of death associated with sepsis. The analyses were by intention-to-treat with univariate survival analysis methods, the log-rank test, and Cox proportional hazards regression. This study is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12613000349741.

Findings—Between March 10, 2010, and Dec 24, 2014, of 20 288 individuals assessed for eligibility, 16 703 participants aged 70 years and older at trial entry were enrolled and followed up for a median of 4·6 years (IQR 3·6–5·6). 8322 (49·8%) participants were assigned to receive aspirin and 8381 (50·2%) to placebo. 203 deaths were considered to be associated with sepsis. Univariate analysis showed similar rates of death associated with sepsis in the two study groups (hazard ratio for aspirin *vs* placebo 1·08, 95% CI 0·82–1·43; p=0·57). Adverse events were previously reported in the ASPREE trial.

Interpretation—Daily low-dose aspirin treatment did not reduce deaths associated with sepsis in community dwelling older adults. Our findings do not support the use of aspirin as a primary prevention strategy to reduce the burden of sepsis in this population.

Introduction

Sepsis is a serious global health problem, with an estimated 49 million incident cases and 11 million related deaths in 2017.[1] Although sepsis-associated mortality is declining in developed countries with ready access to intensive care, risk of mortality remains high if multi-organ failure develops.[2] In May, 2017, the 70th World Health Assembly adopted a resolution for “improving the prevention, diagnosis and clinical management of sepsis”.[3] Within this resolution, primary health care and infection control are the central preventive strategies. The addition of a readily available and cheap drug therapy for the treatment of sepsis could further decrease associated mortality.

Long-term use of low-dose aspirin might reduce mortality in patients with sepsis, as shown in an individual patient data meta-analysis of published observational studies.[4] Several possible underlying mechanisms[5] have been shown through in-vitro,[6,7] animal,[8] and human model[9,10] experiments, which involve pathways such as tumour necrosis factor suppression,[6] lipid mediators of inflammation resolution,[11] and inhibition of platelet activation.[12]

On this basis, we did the Aspirin To Inhibit Sepsis (ANTISEPSIS) trial as a substudy of the ASPirin in Reducing Events in the Elderly (ASPREE) low-dose aspirin primary prevention trial.[13] This study is, to our knowledge, the first randomised clinical trial to examine the potential role of low-dose aspirin use before the onset of severe infection to establish whether this preventive therapy could reduce deaths and hospital admissions attributed to sepsis.

Methods

Study design and participants

We did a randomised, placebo-controlled, double-blind, community-based, clinical trial of low-dose aspirin for the primary prevention of sepsis (ANTISEPSIS). The detailed protocol was published previously.[14] ANTISEPSIS was a substudy of ASPREE—a randomised controlled primary prevention trial of low-dose aspirin compared with placebo on disability-free survival in community dwelling older adults conducted in Australia and the USA—with only Australian participants included in the ANTISEPSIS substudy.[15]

Participants living in Australia and the USA were enrolled in the ASPREE trial if they met the following key inclusion criteria: absence of a life-limiting chronic illness (survival less than 5 years), free from diagnosed cardiovascular disease, dementia or disability, and no major risk of bleeding or aspirin hypersensitivity. ANTISEPSIS investigated prespecified sepsis endpoints in the Australian ASPREE participants only, as insufficient funding was available to include US trial participants. ANTISEPSIS was embedded within the ASPREE trial and relied on its participant monitoring and endpoint data collection. ANTISEPSIS examined sepsis endpoints that were additional to those of the ASPREE trial, which were collected seperately.

Patients provided written informed consent for the ASPREE trial so reconsent was not required for this substudy. Approval for the trial was granted by the Monash University Human Research and Ethics Committee (2006/745MC and CF13/466–2013000204).

Randomisation and masking

In the ASPREE trial,[15] participants were randomly assigned to low-dose, oral aspirin (100 mg per day) or matching placebo. Participants were randomly assigned remotely via the ASPREE web portal according to a computer-generated randomisation schedule, in a ratio of 1:1 to active therapy or placebo. Randomisation of Australian participants was stratified for general practice and age (70–79 years, and age 80 years or older). Variable sized randomisation blocks of two, four, or six were used within strata. ASPREE participants, trial investigators and their staff, and others involved in treating the patients or with data collection and analysis were masked to the identity of the treatment. Treatment was provided in medication bottles labelled with the study participant number only.

Procedures

All ANTISEPSIS endpoint data relied on ASPREE trial processes—ie, participant diaries, in-person visits and scheduled telephone calls to encourage trial retention and collect additional information, retrieval of hospital records, and death certificates. Sepsis was defined as infection plus at least two of the four Systemic Inflammatory Response Syndrome (SIRS) criteria measured during a 24 h period (appendix p 3). The SIRS-based criterion was used as the study design predated the development of the Sepsis-3 definition.[2] Case definitions for specific infectious diseases were used for ANTISEPSIS endpoints. These were derived from published literature describing the diagnostic requirements for pneumonia, urinary tract infection, primary blood stream infection, skin and soft tissue

infection, bone and joint infection, intra-abdominal infection or peritonitis, infective endocarditis, meningitis, gastroenteritis, and influenza (appendix p 3).[14]

Case summaries related to the ANTISEPSIS trial endpoint events were prepared for adjudication from hospital records in which sepsis was described and death certification documents that indicated sepsis as a cause or contributor to death. Hospital records comprised clinical notes, vital sign observations, hospital discharge summaries, and pathology reports. Searches for hospital case records occurred following participant self-report of any hospital admission (in a telephone call every 6 months) or mention of sepsis or infection in other electronic health records. Such records were systematically searched for each participant (eg, general practice notes).

Outcomes

The primary endpoint was met in participants for whom sepsis contributed to their death. If participants died in hospital, hospital records were used to establish whether sepsis was a contributory cause of death. If participants died out of hospital, the death certificate was used to establish whether sepsis was a contributory cause of death. A secondary endpoint was reached when a participant was admitted to hospital due to non-fatal sepsis. Admission to an intensive care unit (ICU) for sepsis, fatal or non-fatal, was another secondary endpoint.

An endpoint event adjudication committee consisting of ANTISEPSIS investigators (four infectious disease physicians and one ICU specialist physician; DPE, ESM, KL, SLM, and DP) established whether potential sepsis episodes met the endpoint criteria. Decision making was facilitated by a module of the ASPREE data suite called AWARD-adjudicator. This module enabled the investigators to independently access and adjudicate de-identified case summary documents via a web application. Both the staff members (EMM and AS) preparing the case summaries and the committee members were masked to treatment group allocation. Two ANTISEPSIS adjudication committee members reviewed each event independently and if there was agreement in endpoint assessment then that was the recorded outcome of the event. If there was discordance between endpoint assessments, then a third reviewer was used to establish the final outcome.

Statistical analysis

The study sample size was calculated assuming a hazard ratio (HR) of 0·63 for the primary endpoint. This effect size was derived from the literature available at the time of our study design, which reported on observed associations between long-term aspirin use and reduced sepsis mortality, and was a conservative estimate.[16,17] Furthermore, it was anticipated that the ASPREE study death rate would be 17·6 per 1000 participant-years (derived from Australian population census data). On the basis of the assumption that 20% of deaths in ASPREE participants would be associated with sepsis,[18] a primary endpoint rate of 3·5 per 1000 participant-years was anticipated for ANTISEPSIS. With a minimum of 16 000 Australian ASPREE participants and an anticipated median follow-up of 4·75 years, accounting for expected dropouts, we would expect 133 primary endpoint events (deaths) in the placebo group. With this number of deaths associated with sepsis, ANTISEPSIS had an 80% power to detect a HR of 0·63 for the aspirin group versus the placebo group. The

secondary endpoint, non-fatal sepsis leading to hospital admission or an episode of infection that developed in hospital was expected to occur more frequently than death due to sepsis.[19] Consequently ANTISEPSIS was powered to detect smaller secondary endpoint effects than outlined above for the primary endpoint.

The analyses were intention-to-treat and used univariate survival analysis methods, the log-rank test, and Cox proportional hazards regression. We did both an unadjusted (univariate Cox proportional hazard for aspirin treatment *vs* placebo) and an adjusted analysis of all endpoint events as per the study protocol.[14] The adjusted proportional hazards analysis included variables selected a priori that were present at the time of randomisation and are known to influence mortality: age, diabetes, current alcohol use, history of cancer, and current smoking (although described in the protocol paper, information on chronic lung disease was not included in the past medical history data collected by ASPREE). In the Cox proportional hazards regression, time to death was used as the primary endpoint. As ANTISEPSIS participants might have had multiple hospital admissions associated with sepsis, the time to the first secondary endpoint was used as the event time. Although several potential secondary endpoint events could not be adjudicated due to unavailability of records, we did not impute missing data as this method is not suitable when outcome variables and explanatory variables are both absent.[20]

In a post-hoc analysis, we analysed individuals whose death we classified as associated with sepsis and reanalysed them stratified according to whether they were classified as death due to cancer in ASPREE. We did this to assess the potential effect of aspirin on death due to sepsis, mediated by cancer.

A Bayesian analysis of the results of this study was done by incorporating a prior probability distribution for the odds ratio of aspirin effect (appendix p 4) based on earlier literature. The prior probability had a mean odds of death when on aspirin compared with placebo of 0·60 (95% credible interval 0·09–2·33). We then updated the prior probability based on the results in our study. Further details are shown in the appendix (p 4).

Bayesian analysis was done with Matlab R2019b. Other analyses were done using Stata, version 15.1. This study is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12613000349741.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. DPE, ESM, and RW had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The ANTISEPSIS substudy included clinical data from the Australian participants from the ASPREE trial aged 70 years and older at trial entry. 20 288 individuals were assessed for eligibility. Participants were enrolled between March 10, 2010, and Dec 24, 2014, and 16

703 were randomly assigned to treatment (figure 1). Of these study participants, 8322 (49·8%) were randomly assigned to receive aspirin and 8381 (50·2%) to receive placebo. The median period of follow-up of participants was 4·6 years (IQR 3·6–5·6) to the time of cessation of the intervention in June 12, 2017. ASPREE was stopped prematurely on this date due to interim analysis showing no benefit of the intervention for the trial's primary outcome.[12] The Australian participants in the ASPREE trial who were studied in ANTISEPSIS were evenly matched at randomisation for age, prevalence of diabetes, smoking, alcohol use, and history of cancer (table 1).

880 potential sepsis events were assessed by the study principal investigators. The number of all events assessed as endpoint events are shown in table 2 (n=616). There were 203 events that met the a priori definition for the study's primary endpoint of death associated with sepsis. Of the remaining assessed events, 413 were classified as hospital admission associated with sepsis, a secondary endpoint. Among these, there were 105 repeated hospital admissions associated with sepsis. 61 (10%) of 616 participants adjudicated to have study endpoints were admitted to the ICU for sepsis. 24 of these patients died. 264 (30%) of 880 potential events that were judged to not be endpoint events were either cases of suspected sepsis or cases in which no sepsis was evident.

Concordance between assessments of potential events was strongest for primary endpoint events, with the two initial adjudicators agreeing on all aspects of the determined outcome in 87·0% (n=203) of instances. For secondary endpoint events, agreement was 80·0% (n=413). Discordant endpoint event assessments mainly involved classification of events not meeting an ANTISEPSIS endpoint (ie, sepsis unproven but suspected and no sepsis), site of infection, or specific pathogenic organism. These were considered by an additional adjudicator and, if still undetermined, were resolved by consensus between four reviewers.

Among all primary and secondary endpoint events, sepsis was predominantly due to pneumonia with smaller numbers of urinary tract infections and bacteraemia. Clinical sites of sepsis and the most common infecting pathogens are described in table 3. *Escherichia coli* was the most common pathogenic bacteria identified. However, most infections, particularly pneumonia, had no pathogen detected. Although sputum microbiology results were often unavailable, absence of a defined causative organism is common in cases of pneumonia and the pneumonia study definition taken from the Infectious Diseases Society of America and American Thoracic Society consensus guidelines[21] does not require microbial identification. Pneumonia diagnoses were confirmed based on clinical parameters including radiographic abnormality (appendix p 3).

There were a total of 912 deaths in the study, of which 203 (22·3%) were attributed to sepsis. Analysis of the primary outcome showed that there were similar numbers of deaths associated with sepsis in participants taking low-dose aspirin and placebo (104 [1·2%] of 8322 in the aspirin group *vs* 99 [1·2%] of 8381 in the placebo group, univariate Cox proportional HR 1·08, 95% CI 0·82–1·43; p=0·57). Overall, 203 (19·8%) of 1024 deaths were associated with sepsis, which was in line with the estimated proportion of deaths associated with sepsis used in power calculations for this study. Adjusting for the study entry variables defined a priori (ie, age, diabetes, current alcohol use, a history of cancer, and

current smoking) did not substantially alter the estimated HR comparing mortality associated with sepsis among participants randomly assigned to low-dose aspirin *vs* placebo (HR 1·06, 95% CI 0·80–1·40; p=0·67). There were no missing covariate data.

There was no evidence of a protective effect of aspirin for the secondary endpoint of hospital admission associated with sepsis (HR 1·18, 95% CI 0·95–1·46; p=0·13). Again, adjusted analysis showed a similar result to the univariate result (HR 1·17, 0·95–1·45; p=0·15). There were few ICU admissions (table 2). Randomisation to aspirin was associated with a non-significant HR of 0·85 (95% CI 0·47–1·51; p=0·58), which showed little change in the adjusted analysis (HR 0·84, 0·47–1·50; p=0·55) for ICU admission.

Although all potential sepsis deaths among ANTISEPSIS participants were adjudicated (n=203), there were many potential hospital admissions associated with sepsis that could not be evaluated due to missing records (450 [33·8%] of 1330 of all potential endpoint events; figure 1). Missing data were not imputed as this method is not suitable when outcome variables and explanatory variables are both absent.

Time to endpoint events among the groups taking low-dose aspirin and placebo is shown by the use of Kaplan-Meier analysis (figure 2). A Bayesian analysis of results provided an update of our prior probability distribution (favouring aspirin benefit) to a posterior probability, suggesting a null effect, with an estimated odds ratio for death in the aspirin group of 1·03 (95% credible interval 0·78–1·35; appendix p 4).

Among the primary endpoint events from this trial (203 deaths associated with sepsis), in post-hoc analysis deaths adjudicated as being due to cancer in the ASPREE trial (76 of the 203 deaths) were not significantly associated with aspirin treatment (p=0·56; appendix p 6). Adverse events were not included as an endpoint in this study as they were reported in the parent trial (ASPREE).

Discussion

In this community based, randomised-controlled trial of older people aged 70 years and older, we showed that a primary prevention strategy using daily low-dose aspirin did not improve endpoints of death or hospital admission associated with sepsis. The relative infrequency of ICU admission could indicate that most sepsis events were mild. The hospital records used for assessments were frequently insufficient to calculate disease severity scores like APACHE II. Parameters including PaO_2 and arterial pH were mostly not available. However, the small number of ICU admissions could also reflect admission policies that exclude older patients with advanced malignancy as was documented in many participants.

The absence of an effect of low-dose aspirin on reducing sepsis endpoints in this study with use of randomised controlled trial data differs from the estimated 7% (95% CI 2–12) improvement in survival derived from a propensity matched analysis of individual patient data from published retrospective observational studies.[4] This meta-analysis included 12 datasets of 6283 patients taking aspirin. The findings were published after ANTISEPSIS commenced and therefore could not be taken into account in our trial design. Aside from the possibility of unmeasured confounders in the retrospective studies included in the meta-

analysis, the severity of the sepsis that occurred in the younger populations of predominantly ICU admitted patients included in the study was greater than in ANTISEPSIS participants.[16,22] It is possible that a primary prevention, randomised, controlled trial involving younger participants than those included in our study could show benefit due to low-dose aspirin's modulation of the immune response to sepsis. However, such a trial would require a prohibitively large sample size due to the infrequency of severe sepsis events.

In addition to no shown benefit in improved sepsis endpoints, long-term aspirin use for primary prevention of sepsis could have the potential to cause harm. In ASPREE, major haemorrhage was more common with aspirin treatment (HR 1·38, 95% CI 1·18–1·62),[23] consistent with findings from an earlier meta-analysis of aspirin primary prevention trials: 58% (odds ratio 1·58, 95% CI 1·29–1·95) increased risk for major gastrointestinal haemorrhage and 27% (1·27, 0·96–1·68) for haemorrhagic stroke.[24] The mean age of patients in studies in the meta-analysis[24] was younger than in our study but doses of aspirin ranged up to 300 mg per day.

It is worth noting apparent differences between the frequency of deaths associated with sepsis in the ASPREE and ANTISEPSIS studies. ASPREE, of which ANTISEPSIS is a substudy, reported on the underlying cause of death and the terminal event that immediately led to death (proximal cause of death) among trial participants, with disability-free survival as the primary endpoint.[13] The ASPREE trial reported an increased all-cause mortality due to low-dose aspirin use (compared with placebo).[25] However, as this was a secondary outcome, the result should be interpreted cautiously. In ASPREE, cancer was the underlying cause in half of deaths (522 [49·6%] of 1052), and also the major contributor to higher mortality in the aspirin group. Death due to sepsis was not a prespecified outcome in the ASPREE study, but this endpoint was included in the group of other deaths (262 [24·9%] of 1052) along with deaths due to chronic lung disease, dementia, and heart failure. No difference in mortality caused by this heterogenous group of diseases was observed between the aspirin and placebo groups.[25]

It was apparent during our study that many deaths judged to be associated with sepsis occurred in participants with advanced malignancy. 76 of the deaths determined to be associated with sepsis in ANTISEPSIS were judged to have cancer as a proximal cause in the ASPREE study. Adjudication of the ANTISEPSIS primary endpoint relied on strict application of the prevailing sepsis definition to establish that infection was either present at admission or developed during the hospital admission that led to death. Given that aspirin was associated with cancer deaths in ASPREE, we did a post-hoc analysis to determine if there was an effect of aspirin in our study, when cancer deaths were considered alone. We found no such effect.

Our study does not appear to have misattributed deaths associated with sepsis with those determined to be due to cancer in the ASPREE trial. We were able to cross reference the cancer deaths from the ASPREE trial that we included in our study and showed that they were not significantly associated with aspirin treatment (appendix p 6).

Underuse of aspirin related to non-adherence to the ASPREE trial intervention could have contributed to the absence of any observed effect on sepsis endpoints. Compliance with medication was 74% for the whole cohort over the median 4·6 years of follow-up; 73% in the aspirin group and 75% in the placebo group.[13] However, with an intention-to-treat analysis, non-adherence is not expected to introduce a systematic bias in results. At the end of year 5 of follow-up, a small number (340 [4·2%] of 8020) of all participants from both treatment and placebo groups who were neither withdrawn from the study nor deceased had taken open-label aspirin, some for a short time.[13] This open-label aspirin use was predominantly due to cardiovascular events. As there was no difference in the use of open-label aspirin between trial groups, this finding is not expected to have had a substantial effect on the ANTISEPSIS study results.

It is not certain as to how long aspirin treatment would need to be taken to achieve a beneficial effect on inflammatory pathways. Human experimental models that showed aspirin mediated reductions in inflammatory responses to noxious stimuli on skin[9] and in the respiratory tract[10] involved patients being treated for 7–10 days before testing. The cellular pathways that might underpin improved sepsis endpoints—reduced tumour necrosis factor expression,[6] increases in lipid mediators of inflammation resolution like aspirin triggered lipoxin,[11] inhibition of platelet activation,[12] and reduced cyclooxygenase production—are affected by aspirin within hours. However, it does appear that for aspirin to reduce sepsis induced inflammation, treatment before infection would be necessary. Commencing aspirin within 24 h after critical illness developed, mostly sepsis, did not prevent development of adult respiratory distress syndrome.[26]

The large sample and thorough assessment of clinical documentation for objective evidence of sepsis are main strengths of the ANTISEPSIS study. There is no potential for allocation bias as adjudicators independently assessed sepsis related events while masked to treatment allocation.

There are several limitations to the ANTISEPSIS study. By showing no benefit of treatment, this study did not provide support for the hypothesis, based on observational data available at the time of protocol design, that aspirin might reduce deaths associated with sepsis (appendix p 4). Although the ANTISEPSIS sample size provided adequate power to detect the estimated effect from the available literature, it might not have had a sufficient number of primary endpoint events to show smaller beneficial or harmful effects of low-dose aspirin. Furthermore, the SIRS-based sepsis definition used in ANTISEPSIS has poor specificity. Notably though, deaths of some participants, which were obviously associated with sepsis on the basis of blood stream infection, were determined as being cases of suspected sepsis and not primary endpoint events as SIRS criteria were not fulfilled. Episodes of severe sepsis in which SIRS criteria are not met is common (12%) and they occur more frequently in people aged older than 70 years.[27]

It was not possible to include community episodes of sepsis that did not lead to hospital admission in ANTISEPSIS as ASPREE participant monitoring was not able to reliably record these events and case definitions could not be assessed. Hence, our secondary endpoints relied on hospital admissions associated with sepsis.

There were few non-white individuals among the Australian participants included in the trial which, in itself, probably reduced the numbers of sepsis endpoint events. Minorities were specifically recruited among US ASPREE participants, although they were not included in the ANTISEPSIS study. Of note, both the rate of sepsis and its associated mortality have been shown to be considerably higher among Black people than white people in the USA,[28] while the global incidence of sepsis and related mortality is highest in sub-Saharan Africa.[1]

Information on whether aspirin had an acute influence on study endpoints was not available as data relating to drug treatment in hospital could not be reliably extracted due to the absence of drug charts. Hospital admissions in which sepsis was community-acquired or health-care associated were not adjudicated separately, which might influence the analysis of this ANTISEPSIS secondary endpoint. Our inability to separate community-acquired and health-care associated sepsis might be of relevance as nosocomial infections such as hospital-acquired pneumonia are more severe than community-acquired pneumonia.[29] Although case ascertainment for deaths associated with sepsis was complete, there were 450 potential secondary endpoint events that could not be evaluated as hospital documents were not available despite strenuous efforts to attain them even after the 5-year study period had concluded.

This trial showed that low-dose aspirin use in individuals older than 70 years did not reduce the rate of death or hospital admissions associated with sepsis. Our analysis does not provide support for the potential benefits of aspirin in reducing sepsis severity seen in previous observational studies. Our negative study result reduces hope for the use of low-dose aspirin as a cheap sepsis prevention strategy and, once again, highlights how crucial it is to undertake prospective randomised trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

Sepsis arising from severe infection is a major cause of death and disability. Treatment of sepsis is costly with varying outcomes, particularly as sophisticated intensive care support is not universally available. An effective and cheap chemoprophylactic strategy could be of major use. Observational studies have shown an association between long-term use of low-dose aspirin and reduced deaths due to sepsis. We searched MEDLINE, Cochrane, and PubMed databases for articles published in any language from database inception to July 1, 2016. A combination of medical subject heading keywords was used. The search terms were “aspirin,” “antiplatelet,” “acetyl-salicylic acid,” “nonsteroidal anti-inflammatory,” “NSAID,” “infection,” “sepsis,” “severe sepsis,” “septic shock,” “mortality,” and “death”. This approach was supplemented with manual reviews of references from included studies. 12 of 15 studies showed a benefit of low-dose aspirin taken before onset of sepsis. Our study-level meta-analysis undertaken using individual patient data from these studies indicated a 7% (95% CI 2–12) reduction in sepsis deaths could be associated with long-term use of low-dose aspirin.

Although this benefit is not traditionally intended as a consequence of preventive therapy, a plausible basis for aspirin’s effect in reducing sepsis deaths is supported by several putative biological mechanisms. These indicate how the drug could affect and reduce inflammatory responses to infection.

Added value of this study

The AspiriN to Inhibit SEPSIS (ANTISEPSIS) study sought to provide, to our knowledge, the first randomised controlled data to explore the potential effect of low-dose aspirin on sepsis deaths. This substudy of the community based, primary prevention ASPREE trial analysed sepsis endpoints that were not included in the parent trial. ANTISEPSIS did not show an effect of low-dose aspirin on deaths or hospital admissions associated with sepsis in a large sample of Australians older than 70 years who were healthy at study entry. Previous results that had shown that low-dose aspirin reduced sepsis deaths are now to be questioned and could have been subject to unmeasured confounders.

Implications of all the available evidence

ANTISEPSIS showed that low-dose aspirin does not improve sepsis outcomes in the study population. These findings provide further evidence against the use of low-dose aspirin for primary prevention in older people, consistent with the ASPREE trial results.

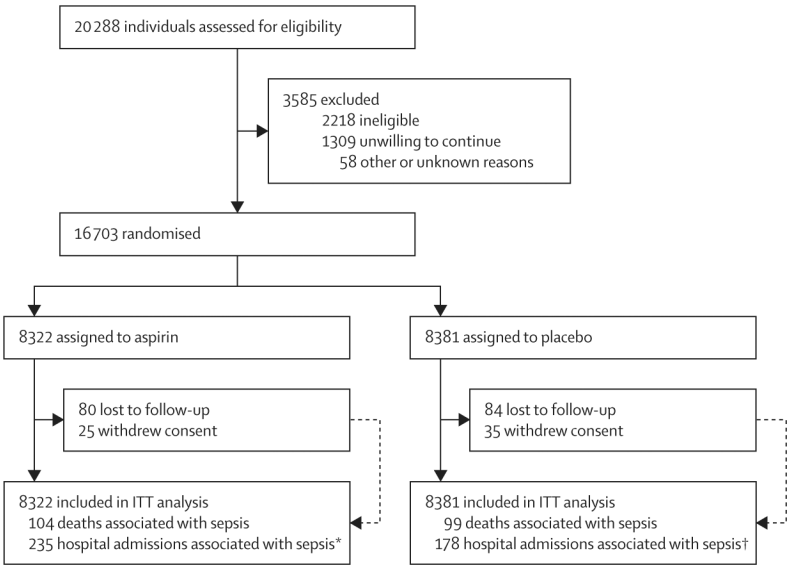

Figure 1: ANTISEPSIS Trial profile

ITT=intention-to-treat. *255 hospital admissions for sepsis event triggers not evaluated. †195 hospital admissions for sepsis event triggers not evaluated.

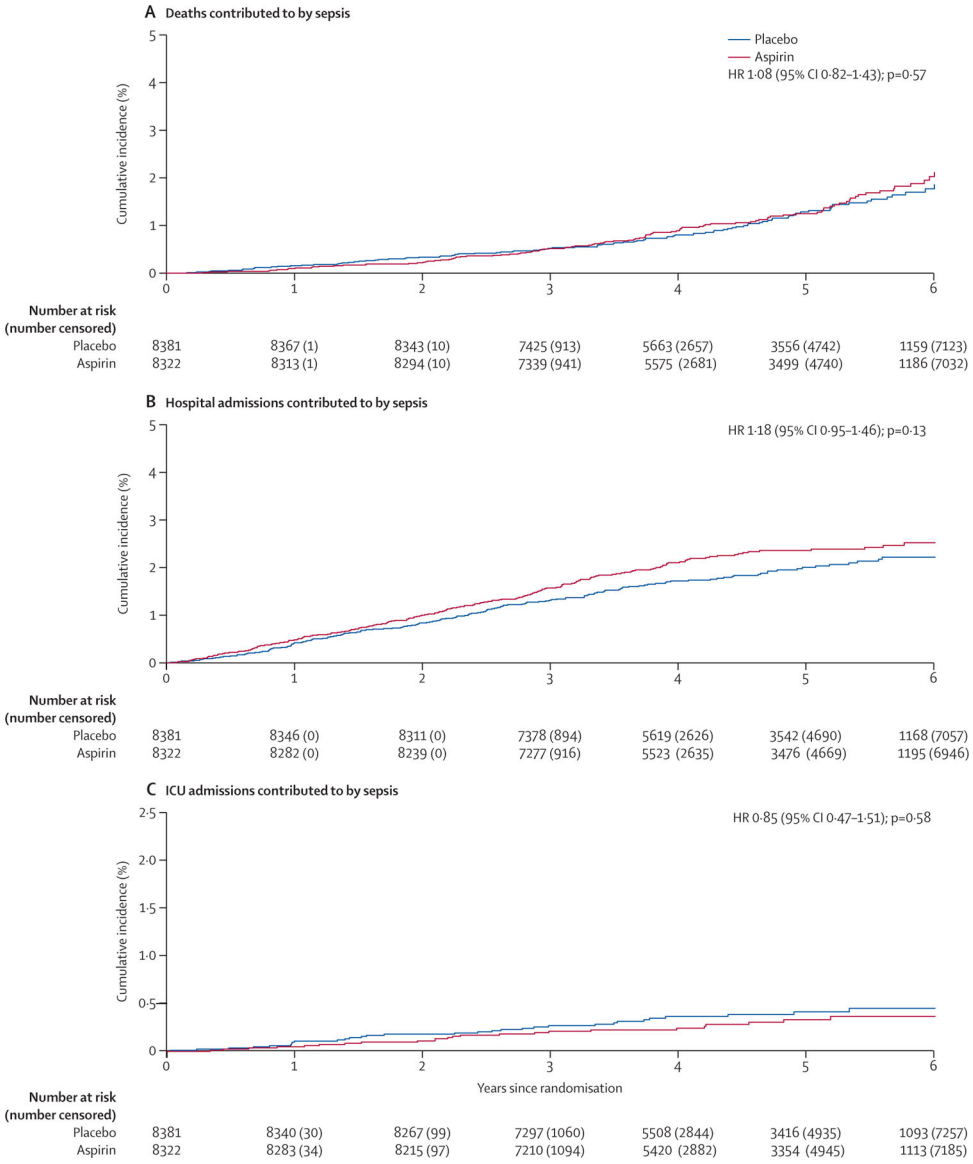

Figure 2: Cumulative incidence of endpoint events

(A) Deaths associated with sepsis. (B) Hospital admissions associated with sepsis. (C) ICU admissions associated with sepsis (note difference in cumulative incidence scale). HR=hazard ratio. ICU=intensive care unit.

Table 1:

Baseline characteristics

	Aspirin (n=8322)	Placebo (n=838l)
Age, years		
70–73	4066 (48·9%)	4141 (49·4%)
≥74	4256 (51·1%)	4240 (50·6%)
Gender		
Women	4571 (54·9%)	4608 (55·0%)
Men	3751 (45·1%)	3773 (45·0%)
Race *		
White	8217 (98·7%)	8254 (98·5%)
Other †	102 (1·2%)	121 (1·4%)
Mean body-mass index, kg/m^2	27·98 (SD 4·64)	27·99 (SD 4·55)
Current smoker	274 (3·3%)	287 (3·4%)
Current alcohol user	410 (4·9%)	404 (4·8%)
Diabetes	701 (8·4%)	666 (7·9%)
Hypertension	6211 (74·6%)	6314 (75·3%)
Dyslipidaemia	5588 (67·1%)	5722 (68·3%)
History of cancer	1617 (19·4%)	1628 (19·4%)
Previous regular aspirin use	605 (7·3%)	604 (7·2%)
Frailty ‡		
Not frail	5097 (61·2%)	5195 (62·0%)
Prefrail	3064 (36·8%)	3037 (36·2%)
Frail	161 (1·9%)	149 (1·8%)
Mean number of days in study	1668·11 (SD 455·40)	1673·25 (SD 453·17)
Median number of days in study	1699 (IQR 1315–2053)	1674 (IQR 1323–2054)

Data are n (%) unless otherwise indicated.

* Missing data in nine participants.

† Aboriginal or Torres Strait Islander race was reported by 12 participants, Pacific Islander or Maori by 11, Asian by 129, Native American by one, Black or African American by four, more than one race by 59, and other by seven.

‡ Frailty was categorised on the basis of the adapted Fried frailty criteria. The category of prefrail included participants who met one or two criteria, and the category of frail included those who met three or more criteria.

Table 2:

Endpoint events

	Aspirin (n=8322)	Placebo (n=838l)	Hazard ratio (95% Cl)	p value
Primary endpoint events				
Deaths	104	99	1·08 (0·82–1·43)	0·57
Secondary endpoint events				
Number of hospital admission events				
1	158 (158)	150 (150)	..	..
2	28 (56)	9 (18)	..	..
3	7 (21)	2 (6)	..	..
4	0 (0)	1 (4)	..	..
Total	235	178	1·18 (0·95–1·46)	0·13
Number of ICU admissions				
1	24 (24)	31 (31)	..	..
2	1 (2)	2 (4)	..	..
Total	26	35	0·85 (0·47–1·51)	0·58

Data are number of participants with events (total number of events) unless otherwise specified. ICU=intensive care unit.

Table 3:

Sites of infection and causative microorganisms

	Urinary tract infection	Pneumonia	Peritonitis	Influenza	Gastroenteritis	Bacteraemia	Infective endocarditis	Bone and joint infection	Meningitis	Skin and soft tissue infection	Other	Total
Primary endpoint events												
Escherichia coli	5	1	0	0	2	3	0	0	0	0	0	11
Enterococci	2	0	0	0	0	0	0	0	0	0	0	2
Klebsiella pneumoniae	1	0	0	0	0	2	0	0	0	0	0	3
Legionella pneumophila	0	1	0	0	0	0	0	0	0	0	0	1
Proteus mirabilis	1	0	0	0	0	0	0	0	0	0	0	1
Staphylococcus aureus	0	3	0	0	0	1	0	0	0	0	1	5
Streptococcus pneumoniae	0	0	0	0	0	2	0	0	0	0	0	2
Streptococcus pyogenes	0	0	0	0	0	0	0	0	0	2	0	2
Other	1	6	1	0	0	2	0	0	0	0	3	13
Not identified	6	133	10	0	1	0	2	0	0	1	10	163
Total	16	144	11	0	3	10	2	0	0	3	14	203
Secondary endpoint events												
Bacteroides fragilis	0	0	0	0	1	1	0	0	0	0	0	2
Clostridioides difficile	0	0	0	0	2	0	0	0	0	0	0	2
Escherichia coli	48	0	2	0	0	13	0	0	0	1	1	65
Enterococci	6	1	1	0	0	2	1	0	0	0	0	11
Haemophilus influenzae	0	3	0	0	0	1	0	0	0	0	0	4
Klebsiella pneumoniae	2	1	0	0	0	4	0	0	0	0	0	7
Neisseria meningitidis	0	0	0	0	0	0	0	0	1	0	0	1
Proteus mirabilis	4	1	0	0	0	1	0	0	0	0	0	6
Staphylococcus aureus	0	4	0	0	0	5	0	2	0	3	2	16

	Urinary tract infection	Pneumonia	Peritonitis	Influenza	Gastroenteritis	Bacteraemia	Infective endocarditis	Bone and joint infection	Meningitis	Skin and soft tissue infection	Other	Total
Salmonella enteritidis	0	0	0	0	3	0	0	0	0	0	0	3
Streptococcus pneumoniae	0	7	0	0	0	0	0	0	0	0	1	8
Streptococcus pyogenes	0	0	0	0	0	2	0	0	0	0	0	2
Viridans streptococci	0	0	0	0	0	2	1	0	0	0	0	3
Influenza	0	0	0	8	0	0	0	0	0	0	0	8
Other	16	10	0	0	5	18	0	2	1	5	0	57
Not identified	4	167	14	0	1	0	0	5	0	18	9	218
Total	80	194	17	8	12	49	2	9	2	27	13	413