British Cardiovascular Society

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Aspirin use in the primary prevention of cardiovascular events – 3 strikes and out?

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Take Home Messages

- Cardiovascular disease (CVD) costs the NHS an estimated **£9 billion** per year and causes **26%** of all deaths in the UK
- Aspirin largely has an evidence base in the secondary prevention of CVD, with limited data available in a primary prevention setting
- This editorial evaluates 3 recently published pivotal trials investigating the role of aspirin in the primary prevention of CVD; ARRIVE, ASCEND, and ASPREE
- ARRIVE and ASPREE did not demonstrate a reduction in cardiovascular events with aspirin, whilst ASCEND showed benefit in patients with diabetes mellitus
- All 3 trials demonstrated a significant increase in major bleeding and therefore **aspirin therapy is NOT recommended in the primary prevention of CVD**

Introduction

Aspirin (acetylsalicyclic acid) has proven benefit in the secondary prevention of coronary and cerebrovascular events.(1, 2) However, its role in the primary prevention of cardiovascular events remains controversial. Whilst several earlier studies have supported a reduction in the incidence of myocardial infarction and stroke(3-8), more recent studies have not been so convincing.(9-12) A meta-analysis of almost 100,000 patients demonstrated aspirin therapy to be associated with a 12% reduction in the risk of serious vascular events (95% confidence interval, 6 to 18), but this was offset by a 50% increase in bleeding.(2) As a result, conflicting information is seen in published guidelines; the U.S. Preventive Services Task Force recommends the use of aspirin in primary prevention of cardiovascular events in certain individuals (13) whilst the European Society of Cardiology and NICE guidelines discourage its use. (14, 15)

Three large randomised controlled trials (RCT's) investigating the effects of aspirin for primary prevention have been published in recent months that contribute to the evidence base:

ARRIVE – Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease.

ARRIVE (16) was a randomised, double blind, placebo controlled study conducted in seven countries (Germany, Italy, Ireland, Poland, Spain, UK, and the USA). The inclusion criteria varied between male and female patients: male patients ≥ 55 years of age required between 2

and 4 risk factors (RF's); female patients ≥ 60 years of age required 3 or more RF's. Participants had a moderate cardiovascular risk (10-year coronary heart disease and cardiovascular disease risk of 10-20% and 20-30% respectively). Risk factors included total cholesterol >5.180 mmol/L for men and >6.126 mmol/L for women, LDL> 3.367 mmol/L for men and > 4.144 mmol/L for women, HDL< 2.2 mmol/L, any smoking within the preceding 12 months, systolic blood pressure > 140 mmHg or requirement for anti-hypertensive medication, and positive family history of cardiovascular disease. Exclusion criteria included a history of previous stroke, myocardial infarction, coronary artery angioplasty or stenting, coronary artery bypass graft, relevant arrhythmias, congestive heart failure, vascular intervention, requirement for antiplatelet therapy / anticoagulants, high risk of gastrointestinal (GI) or other bleeding, gastric or duodenal ulcers, GI bleeding, frequent use of nonsteroidal anti-inflammatory drugs, and diabetes mellitus.

The primary efficacy endpoint was a composite of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, and transient ischaemic attack. Secondary endpoints included a composite of time to first occurrence of cardiovascular death, myocardial infarction, and stroke; time to and incidence of all-cause mortality; time to individual components of the composite primary endpoint. The safety endpoint included haemorrhagic events.

A total of 12,546 patients were randomised to either 100 mg enteric-coated aspirin (n=6270) or placebo (n=6276) at 501 sites and followed up for 5 years. Premature termination from the study was similar in both groups (29.4% in the aspirin group versus 29.9% in the placebo group). Common reasons for termination included withdrawal, lost to follow-up, and death (no significant difference between the two groups).

In the intention-to-treat analysis, the primary endpoint occurred in 4.29% of 6270 patients in the aspirin group and 4.48% of 6276 patients in the placebo group [HR 0.96, p=0.6038]. Fatal and non-fatal myocardial infarction occurred in 1.52% of patients in the aspirin group and 1.78% of the placebo group [HR 0.85, p=0.2325]. In the per-protocol analysis (at least 60% compliant), the primary endpoint occurred in 3.40% of 3790 patients in the aspirin group and 4.19% of 3912 patients in the placebo group [HR 0.81, p=0.0756]. The HR's for total myocardial infarction [HR 0.53, p=0.0014] and non-fatal myocardial infarction [HR 0.55, p=0.0056] were lower with aspirin therapy.

The death rate was 2.55% in the aspirin group and 2.57% in the placebo group [HR 0.99, p=0.9459]. Gastrointestinal bleeding occurred in 0.97% of patients in the aspirin group and 0.46% of the placebo group [HR 2.11, p=0.0007]. The vast majority of gastrointestinal bleeding events were categorised as mild and there was no significant difference in fatal bleeding rates

between the two groups. Of note, severe gastrointestinal bleeding occurred in 0.06% of the aspirin group and 0.03% of the placebo group.

Aspirin did not lower the risk of major cardiovascular events in the ARRIVE cohort despite this being a population with multiple risk factors and allegedly at moderate risk of cardiovascular events. However, the event rate was significantly lower than anticipated at less than 10% over 10 years and therefore more in keeping with a low risk population. These findings can likely be explained by contemporary management of risk factors. The per-protocol analysis for total and non-fatal myocardial infarction demonstrated benefit with aspirin use but this has to be carefully balanced with the increased risk of bleeding, albeit mild in the majority of cases. Moreover, per-protocol analysis can weaken the power of randomisation and introduce unmeasured confounding.

ASCEND – A Study of Cardiovascular Events in Diabetes.

ASCEND (17) was a randomised, double blind, placebo controlled study. Men and women ≥ 40 years of age, a diagnosis of diabetes mellitus, no known cardiovascular disease, and uncertainty regarding the benefit of aspirin therapy were eligible for recruitment. Exclusion criteria included a clear indication or contraindication to aspirin therapy or clinical conditions that would limit participant follow-up for at least 5 years.

The primary efficacy endpoint was the first serious vascular event which was defined as a composite of non-fatal myocardial infarction, non-fatal stroke (excluding intracranial haemorrhage), transient ischaemic attack, or death from any vascular cause (excluding intracranial haemorrhage). The primary safety endpoint was the first occurrence of any major bleeding event. This was defined as a composite of any confirmed intracranial haemorrhage, sight-threatening bleeding event, gastrointestinal bleeding, or any other serious bleeding event. Secondary endpoints included gastrointestinal cancer, a composite of any serious vascular event, or any arterial revascularisation procedure. Trial participants were categorised into 3 groups depending on their baseline 5-year vascular risk: less than 5%, 5% to less than 10%, and 10% or more.

A total of 15,480 patients were randomised to aspirin (n=7740) or placebo (n=7740) and followed up for a mean interval of 7.4 years. There was no significant difference in the discontinuation of the trial regimen between the two groups. The primary efficacy endpoint occurred in 8.5% of the aspirin group and 9.6% of the placebo group [Hazard ratio 0.88, p=0.01]. Interestingly, the improvement in risk was only evident within the first 5 years following randomisation. There was no difference between the two groups with respect to death from any vascular causes.

There was a significantly increased incidence of major bleeding in 4.1% of the aspirin group compared to 3.2% of the placebo group [hazard ratio 1.29, p=0.003]. The majority of these bleeding events were gastrointestinal [41.3%], sight threatening [21.1%], and intracranial haemorrhages [17.2%]. The incidence of fatal bleeding events in the aspirin group [0.2%] and the placebo group [0.2%] in addition to the incidence of haemorrhagic stroke in the aspirin group [0.3%] and the placebo group [0.3%] were similar. Finally, there was no difference between the two groups in the risk of gastrointestinal tract or any other type of cancer.

The aspirin group demonstrated a 12% relative risk reduction in vascular events and a corresponding 29% increase in the risk of major bleeding. Exploratory analysis comparing participants of varying baseline vascular risk (<5%, 5% to <10%, and ≥ 10%) identified no significant difference with respect to incidence of serious vascular events or bleeding. In summary, aspirin therapy reduced serious vascular events in patients with diabetes mellitus and no known cardiovascular disease, but this benefit was offset by increased major bleeding.

ASPREE – Aspirin in Reducing Events in the Elderly

ASPREE (18-20) was a randomised, double blind, placebo controlled trial that recruited participants from 34 sites in the United States and 16 sites in Australia. Participants were ≥ 70 years of age (or ≥ 65 years of age among blacks and Hispanics in the United States) with no history of cardiovascular disease, dementia, physical disability, or any illness that would result in less than 5-years of survival. Exclusion criteria included a diagnosis of dementia, substantial physical disability, high risk of bleeding, requirement for anticoagulation, or contraindication to aspirin therapy.

The primary endpoint was defined as survival-free from dementia or persistent physical disability. The primary composite endpoint consisted of first occurrence of death, dementia, and persistent physical disability. The secondary endpoints included the three individual components of the composite primary endpoint. Other secondary endpoints included a composite of cardiovascular disease (fatal coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal stroke, or hospitalisation from heart failure), fatal and non-fatal cancer, mild cognitive impairment, depression, and major haemorrhage (composite of haemorrhagic stroke, symptomatic intracranial bleeding, bleeding requiring transfusion, hospitalisation, prolonged hospital stay, surgery, or death).

A total of 19,114 patients were randomised to the aspirin group [n=9525] or the placebo group [n=9589]. The rate of adherence to the assigned intervention was similar with 62.1% in the aspirin group and 64.1% in the placebo group. The primary composite endpoint of death,

dementia, or physical disability occurred in 921 participants of the aspirin group and 914 participants of the placebo group [HR 1.01, p=0.79]. The secondary individual endpoint of all-cause-death occurred in 558 participants of the aspirin group and 494 participants of the placebo group [HR 1.14, unadjusted 95% CI, 1.01 to 1.29]. There was no significant difference in the rate of dementia or persistent physical disability between the aspirin group and placebo group; the rate of dementia was 6.7 events per 1000 person-years in the aspirin group and 6.9 events per 1000 years in the placebo group [HR 0.98, 95% CI 0.83 to 1.15]; the rate of persistent physical disability was 4.9 events per 1000 person-years in the aspirin group and 5.8 events per 1000 person-years in the placebo group [HR 0.85, CI 0.70 to 1.03].

The composite secondary endpoint for cardiovascular disease was similar between the aspirin group (10.7 events per 1000 person-years) and the placebo group (11.3 events per 1000 person-years – HR 0.95, CI 0.83 to 1.08). No individual component of this endpoint demonstrated any significant difference between the two groups. The rate of major haemorrhage was 8.6 events per 1000 person-years in the aspirin group and 6.2 events per 1000 person-years in the placebo group [HR 1.38, 95% CI 1.18 – 1.62, P<0.001]. Upper gastrointestinal bleeding [HR 1.87, 95% CI 1.32 to 2.66] and subdural or extradural haemorrhage [HR 1.79, 95% CI 1.06 to 3.02] were particularly pronounced in the aspirin group relative to the placebo group. Finally, there was no difference with respect to fatal bleeding with less than 1 event per 1000 person-years in both groups.

The risk of death from any cause was 12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group [HR 1.14, 95% CI 1.01 to 1.29]. Interestingly, the increased risk of death in the aspirin group was largely related to an underlying diagnosis of cancer. The risk of cancer-related death was 6.7 events per 1000 person-years in the aspirin group and 5.1 events per 1000 person-years in the placebo group [HR 1.31, 95% CI 1.10 to 1.56]. This was an interesting finding not in keeping with previous trial data on the effect of aspirin on cancer mortality. (21) The mechanism remains unclear but may be related to a lower number of elderly patients in previous studies, or an age dependent biological mechanism yet to be elucidated completely.

In summary, the ASPREE trial demonstrated that aspirin therapy does not prolong disability-free survival nor reduce adverse cardiovascular outcomes. Furthermore, all-cause mortality was increased in the aspirin group and primarily driven by cancer-related deaths. Finally, despite careful selection criteria, participants in the aspirin group experienced a significantly higher rate of major haemorrhage compared to the placebo group.

Conclusion

The ARRIVE and ASPREE trials do not demonstrate any significant evidence to support aspirin therapy for primary prevention of cardiovascular events, whilst the ASCEND trial did demonstrate benefit in a diabetic cohort. All 3 trials revealed a significantly increased risk of major haemorrhage. Although a previous meta-analysis has suggested a protective effect of aspirin therapy with respect to cancer, this was not seen in the ARRIVE or ASCEND trials. Moreover, the ASPREE trial demonstrated increased mortality with aspirin therapy. Overall, on the basis of these latest data, aspirin therapy for primary prevention of cardiovascular events is generally not recommended but the risk-benefit ratio should be determined for each individual patient.

Future Perspectives

A recent meta-analysis has suggested the efficacy of low-dose aspirin (75-100 mg) to reduce cardiovascular events is dependent on body weight; individuals weighing 50-69 kg demonstrated benefit [HR 0.75, CI 0.65-0.85] whilst those weighing ≥ 70 kg had no benefit [HR 0.95, CI 0.86-1.04].(22) Therefore, further clinical trials are required to investigate the role of aspirin therapy, including variable weight-dependent dosing, on both the primary prevention of cardiovascular events and also potentially cancer. Finally, given the lack of evidence supporting aspirin use in primary prevention, a study conducted in the context of contemporary risk factor modification may be necessary to confirm the benefit in a secondary prevention setting. However, relatively recent data from the PEGASUS-TIMI 54 and DAPT studies suggest anti-platelet therapy can provide incremental benefit in this population. (23, 24)

Study	Population	Intervention	Primary Endpoint	Secondary Endpoint	Results
ARRIVE Randomised, double blind, placebo controlled study n = 12,546	Men ≥ 55 with 2 to 4 risk factors Women ≥ 60 with 3 or more risk factors Moderate risk of CVD (10-year risk 20-30%)	Enteric coated Aspirin 100 mg versus Placebo	Composite of time to first occurrence of: - Cardiovascular death - MI - Unstable angina - Stroke - Transient ischaemic attack	Composite of time to first occurrence of: - Cardiovascular death - MI - Stroke Time to and incidence of all-cause mortality; Time to individual components of the composite primary endpoint Safety Endpoint: Haemorrhagic events	**Intention to treat analysis:** Primary Endpoint: Aspirin group (4.29%), Placebo group (4.48%) HR 0.96, p = 0.6038 **Per protocol analysis:** Primary Endpoint: Aspirin group (3.40%), Placebo group (4.19%) HR 0.81, p = 0.0756 Secondary Endpoint: Total MI (HR 0.53, p = 0.0014) Non-fatal MI (HR 0.55, p = 0.0056) **Safety Endpoint (**Gastrointestinal bleeding): Aspirin group (0.97%), Placebo group (0.46%) HR 2.11, p = 0.0007
ASCEND Randomised, double blind, placebo controlled study n = 15,480	Men and woman ≥ 40 - Diabetes mellitus - No known CVD	Enteric coated Aspirin 100 mg versus Placebo	**Efficacy endpoint** was the first serious vascular event defined as a composite of: - Non-fatal MI - Non-fatal ischaemic stroke - Transient ischaemic attack - Death from any vascular cause Safety endpoint: major bleeding defined as a composite of: - Any confirmed intracranial haemorrhage - Sight-threatening bleeding event - Gastrointestinal bleeding - Any other serious bleeding event	Gastrointestinal cancer; Composite of any serious vascular event; Arterial revascularisation procedure	**Primary efficacy endpoint:** Aspirin group (8.5%), Placebo group (9.6%) HR 0.88, p=0.01 **Safety Endpoint:** Incidence of major bleeding: Aspirin group (4.1%), Placebo group (3.2%) HR 1.29, p = 0.003
ASPREE Randomised, double blind, placebo controlled study n = 19,114	Men and women ≥ 70 with no history of: - CVD - Dementia - Physical disability	Enteric coated Aspirin 100 mg versus Placebo	Survival-free from: - dementia or persistent physical disability The primary composite endpoint consisted of: - First occurrence of death - Dementia - Persistent physical disability	Individual components of the composite primary endpoint; Composite of CVD - Fatal coronary heart disease - Non-fatal MI - Fatal or non-fatal stroke - Hospitalisation from heart failure Fatal and non-fatal cancer; Mild cognitive impairment; Depression; Major haemorrhage	**Primary Endpoint:** Aspirin group (921 participants), Placebo group (914 participants) HR 1.01, p = 0.79 **Secondary Endpoint:** **All-cause-death:** Aspirin group (558 participants), Placebo group (494 participants) HR 1.14, CI 1.01 to 1.29 **Cardiovascular disease:** Aspirin group (10.7 events per 1000 person-years), Placebo group (11.3 events per 1000 person-years) HR 0.95, CI 0.83 to 1.08) **Major haemorrhage:** Aspirin group (8.6 events per 1000 person-years), Placebo group (6.2 events per 1000 person-years) HR 1.38, 95% CI 1.18 – 1.62, P<0.001] **All-cause mortality** Aspirin group (12.7 events per 1000 person-years), Placebo group (11.1 events per 1000 person) HR 1.14, 95% CI 1.01 to 1.29]

CVD: cardiovascular disease; MI: myocardial infarction; HR: hazard ratio; CI: confidence interval

Table 1. Summary of clinical trial results.

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