

ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events): A Study to Assess the Efficacy and Safety of Aspirin in Patients at Moderate Risk of Cardiovascular Disease

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ARRIVE Executive Committee: *JM. Gaziano, C. Brotons, R. Coppolecchia, C. Cricelli, H. Darius, PB. Gorelick, G. Howard, TA. Pearson, PM. Rothwell, LM. Ruilope, M. Tendera, G. Tognoni.*

Declaration of Interest

- Consulting/Royalties/Owner/Stockholder of a healthcare company (Consulting-Bayer)
- All voting members of the ARRIVE Executive Committee (EC) received personal fees from Bayer during the conduct of the study.
- R. Coppolecchia is an employee of Bayer Healthcare.
- The following EC members report additional relationships:
 - PMR: personal fees from Bristol-Meyers Squibb
 - LMR: personal fees from Novartis, Sanofi, Medtronic, Daiichi-Sanyo and grants from Astra-Zeneca
 - MT: personal fees from Celyad, Janssen Cilag, Kowa, Perfuse Group, Servier
- Role of the sponsor and executive committee are provided in detail in the paper in the *Lancet*.

Conclusions

- The ARRIVE trial attempted to address the role of low-dose aspirin in primary prevention of CV events in subjects at moderate levels of CV risk in a pragmatic primary care-based randomized trial.
- Results showed aspirin treatment did not significantly reduce the rate of CV events in the intent-to-treat study population (HR 0.96; 95% CI 0.81-1.13; P=0.60).
- Effects on specific outcomes such as first heart attack were generally consistent with previous studies with low-dose aspirin.
 - Analyses in patients who completed their treatment according to protocol demonstrated a significant reduction in risk of a first heart attack
 - No effects were seen on risk of a first stroke.
- Safety results also were consistent with previous primary prevention studies demonstrating an increased risk (HR 2.11, 95% CI 1.36-3.28; P=0.0007) at a very low rate of predominantly mild GI bleeding with low-dose aspirin. There was no difference in fatal bleeding rates between aspirin and placebo.
- ARRIVE demonstrates the challenges of conducting long-term primary prevention trials in an era of aggressive management of risk factors among higher risk individuals in the current era with the availability of preventive and treatment measures. However, ARRIVE adds to the available data more information about older information and women.
- The use of aspirin remains a decision that should involve a thoughtful discussion between a clinician and a patient given the need to weigh the CV and cancer benefits against the bleeding risks, patient preferences, cost, and other factors.

Background

- The role of acetylsalicylic acid (aspirin) has been well established in the acute treatment and secondary prevention of coronary and cerebrovascular diseases.
 - More than 200 trials involving 200,000+ patients support use of low-dose aspirin in acute setting of MI and ischemic stroke or among those with cardiovascular disease such as MI, ischemic stroke, transient ischemic attack, CAD, and PVD
 - Clinical guidelines and government agencies generally support the use of low-dose aspirin in these settings.
- However, the use of aspirin in the primary prevention of acute coronary and cerebrovascular events remains controversial and major guidelines regarding low-dose aspirin use in this setting are inconsistent. There are far fewer primary prevention trials and most were done among those at low CVD risk.
- The ARRIVE trial was designed to assess the efficacy and safety of 100 mg enteric-coated aspirin tablets (once daily) versus placebo in subjects with a moderate estimated risk (20-30% 10-year CVD risk, 10-20% CHD risk) of for a first acute CV event.

Purpose and key points about methods

- ARRIVE was a randomized, double-blind, placebo-controlled, primary care based, multicenter trial, carried out in 7 countries (Germany, Italy, Ireland, Poland, Spain, UK, and US).
 - Follow-up was conducted by primary care physicians at face-to-face visits, through phone calls, and by obtaining medical records which were submitted for adjudication.
- Target study population: Subjects without known CV disease or diabetes, but with an average estimated 10-year CV disease risk of approximately 20-30% (10-20% 10-year CHD risk) based on European and US risk calculators.
 - Men ≥ 55 years with 2 or more CV risk factors
 - Women ≥ 60 years with 3 or more CV risk factors
- Primary efficacy endpoint: Time to first occurrence of a composite of CV death, myocardial infarction (MI), unstable angina (UA), stroke and transient ischemic attack (TIA)
- Secondary endpoints: A composite of CV death, MI or stroke, all-cause death, and incidence of components of the primary endpoint
- Safety endpoints: Bleeding events and incidence of adverse events

Results

- A total of 12,546 (mean age 64 years; nearly 30% women) patients were randomized to receive aspirin (N=6270) or placebo (N=6276). The median follow-up was 60 months.
- While estimate 10-year CV risk was over 17%, the observed CV event rates were considerably less than anticipated, corresponding to a lower risk population with a 10-year event rate <9%.
- In the ITT analysis, the primary endpoint occurred in 269 individuals in the aspirin group (4.29%) versus 281 (4.48%) in the placebo group (Hazard Ratio (HR) 0.96; 95% CI 0.81-1.13; p=0.60).
- In the per-protocol analysis, aspirin reduced the risk of a first MI by 47% (HR 0.53; 95% CI 0.36-0.79; p=0.0014). The risk of a first non-fatal MI was reduced by 45% (HR 0.55, 95% CI 0.36-0.84; p=0.0056).
- Gastrointestinal bleedings (mostly mild) occurred in 61 (0.97%) patients in the aspirin group versus 29 (0.46%) in the placebo group (HR 2.11; 95% CI 1.36-3.28; p=0.0007, ITT population). No difference in fatal bleeding rates was observed.
- No effects were seen on short-term cancer rates; the length of follow-up was insufficient to assess longer-term outcomes.



Key messages

- While no overall reduction was observed in the primary composite endpoint of CV events, results from ARRIVE are generally consistent with many other studies that tended to demonstrate aspirin's ability to lower the risk of first nonfatal MI without affecting risk of total stroke.
- Safety results also were consistent with previous studies showing an increased risk, at a low rate of GI bleeds.
- ARRIVE demonstrates challenges of conducting long-term primary prevention trials in the current era of aggressive management of CV risk factors and treatment which may lower event rates.
- ARRIVE adds relevant information on efficacy and safety of aspirin in primary prevention of CVD adding more data on older individuals and women. More data are coming from other completed trials.
- The use of aspirin remains a decision that should involve a thoughtful discussion between a clinician and a patient given the need to weigh the CV and cancer benefits against the bleeding risks, patient preferences, cost, and other factors.