



# Aspirin: Trial Updates Science Awards 2018

ASPREE

ASCEND

AspECT

seAFood

ARRIVE



# Aspirin: Trial Updates and Science Awards 2018

## connections, debate, questions and clarity

The International Aspirin Foundation's meeting held at The Royal Society of Edinburgh very much lived up to the motto of this institution; "Knowledge made useful." In addition to recognising the valuable work of the winners of the Emerging Aspirin Investigator Award and the Senior Science Award, the Principal Investigators from five of the recently completed major aspirin trials (ARRIVE1, ASCEND2, ASPREE3-5, AspECT6 and seAFOod7) presented and discussed their findings. The attendees, an international, multidisciplinary group of scientists and clinicians including professors of neurology, epidemiology, gastroenterology, oncology and pharmacology, gave great value in terms of intense debate and the sharing of knowledge.

Pippa Hutchison, Executive Director of the International Aspirin Foundation, gave a warm welcome to attendees and in particular, thanked the Principal Investigators of the recently completed aspirin trials who travelled from as far as Australia in order to be part of this unique meeting.

Professor Carlo Patrono, Chair of the Scientific Advisory Board for the International Aspirin Foundation opened the meeting with a poignant step back in time through the pedigree of previous award winners. Professor Patrono dedicated his presentation to the memory of Gustav Born, a good friend and a great scientist, who received the Aspirin Senior Award in 1995 for his seminal work on platelet physiology. Carlo expressed sadness at the loss of this 'intense human and scientific life'.





# Senior Science Award

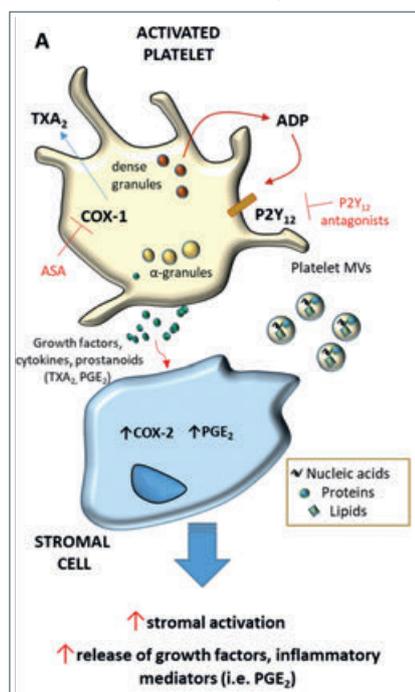
Professor Peter Rothwell presented Professor Paola Patrignani, Professor of Pharmacology from the University of Chieti, Italy, with the Senior Science Award and described how she is a leader in the field of arachidonic acid metabolism and the pharmacology of antiplatelet and anti-inflammatory drugs. Professor Patrignani's work has made a major contribution to the understanding of the biosynthesis, biochemistry and molecular biology of the COX-pathway and downstream enzymes.

The intricacies of aspirin's pharmacological activity within the body were presented by Professor Paola Patrignani in her award acceptance presentation and this in many ways helped to inform some of the results from the presentations that followed in the clinical trials update session. A clear theme of 'one size does not fit all' resonated throughout the meeting and the insight gained from Paola's award-winning work helps to explain this. Professor Patrignani's work includes the development of a direct biomarker of aspirin activity making it possible to study what is happening within the individual and may potentially lead to a better understanding of how best to dose aspirin for different populations of patients. Her work demonstrates the feasibility of quantifying the extent and duration of platelet COX-1 acetylation and shows how this can enable the characterisation of the genetic, pharmacokinetic and pharmacodynamic determinants of interindividual variability in the antiplatelet response to low dose aspirin and has helped to identify extra-platelet sites of aspirin drug activity.

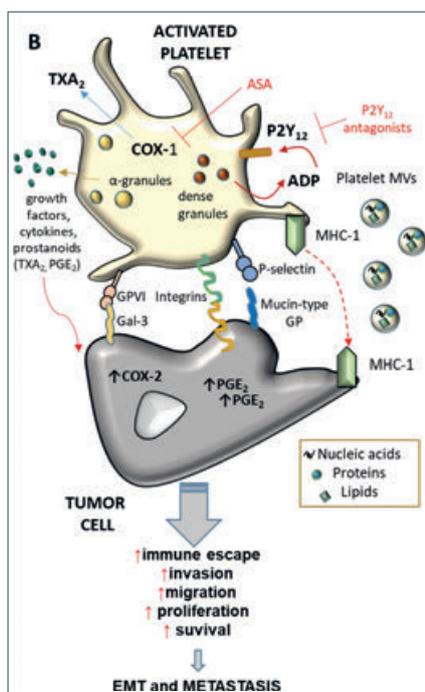
In addition, Professor Patrignani showed how her work has helped to translate the clinical findings of aspirin's cancer prevention benefits into a mechanistic hypothesis of aspirin's anti-cancer effects: aspirin is thought to affect early events in intestinal tumorigenesis. Paola proposed that crosstalk between platelets and stromal cells in the intestine appear to promote a chronic inflammatory response which may then lead onto colorectal cancer (CRC) development. Low-dose aspirin selectively inhibits platelet function and it is in this way that it may constrain the pro-inflammatory role of platelets in cancer development.

## The crucial roles of platelets in cancer

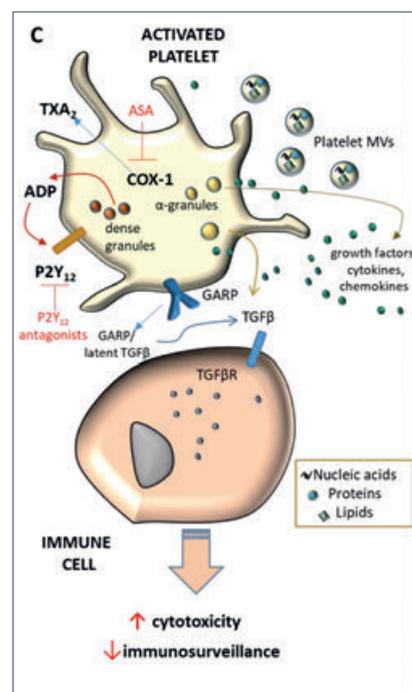
### Early events of tumorigenesis



### Metastasis



### Tumour immune escape



Contursi, Grande & Patrignani et al. Biochemical Society Transactions, 2018

In the case of cancer metastatic spread, it is thought that platelet and cancer cell interactions increase the metastatic potential of a tumour by increasing the tumour's ability to migrate and survive. Professor Patrignani explored the role of tumour educated platelets (TEPs) in which a platelet phenotype change occurs making them more able to facilitate the spread of metastases around the body. By inhibiting platelets, aspirin reduces the metastatic potential of cancer cells.

In addition to the inhibition of early events in tumorigenesis and the potential reduction in metastatic spread, aspirin can also help stop tumour immune escape and may be useful in combination with cancer immune therapies. Professor Patrignani showed how her work has helped to explain all these mechanisms in terms of pharmacological activity.

In the future Professor Patrignani hopes to use the novel direct biomarker of aspirin action to help understand the extent of acetylation of COX-1 and COX-2 in the CRC lesions of patients taking low and medium doses of aspirin. Work that may in turn lead to a better understanding of the ideal dosing strategy to use.

During the discussion the role of factors such as obesity were explored. It is understood that obesity increases platelet activity and this is one mechanism by which obesity increases the risk of developing CRC.

**Watch a short interview with Professor Rothwell and Professor Patrignani here:**

<https://www.aspirin-foundation.com/scientific-awards/senior-science-award-2018/>



# Emerging Aspirin Investigator Award

The Emerging Aspirin Investigator Award was presented by Dr Andrew Chan. He acknowledged the quality and diversity of the submissions received by the Scientific Advisory Board (SAB) for the award, and the significance this body of work has for our understanding of aspirin use in chronic disease prevention. The impact from the work of this year's winner Dr Steven Dehmer, a health economist from the USA, is already being felt with his cardiovascular disease (CVD) microsimulation model which was pivotal to the 2016 United States Preventative Services Task Force (USPSTF) recommendations. The model simulated almost one billion life years of data, in order to be able to identify the net benefit-harm balance point, where aspirin is advantageous to different sub groups of the population for primary disease prevention. The SAB looks forward to following Dr Dehmer in his future career as he continues his modelling work to guide clinicians in aspirin use.

[Watch a short interview with Dr Chan and Dr Dehmer here:](https://www.aspirin-foundation.com/scientific-awards/emerging-investigator-award-2018/)

<https://www.aspirin-foundation.com/scientific-awards/emerging-investigator-award-2018/>





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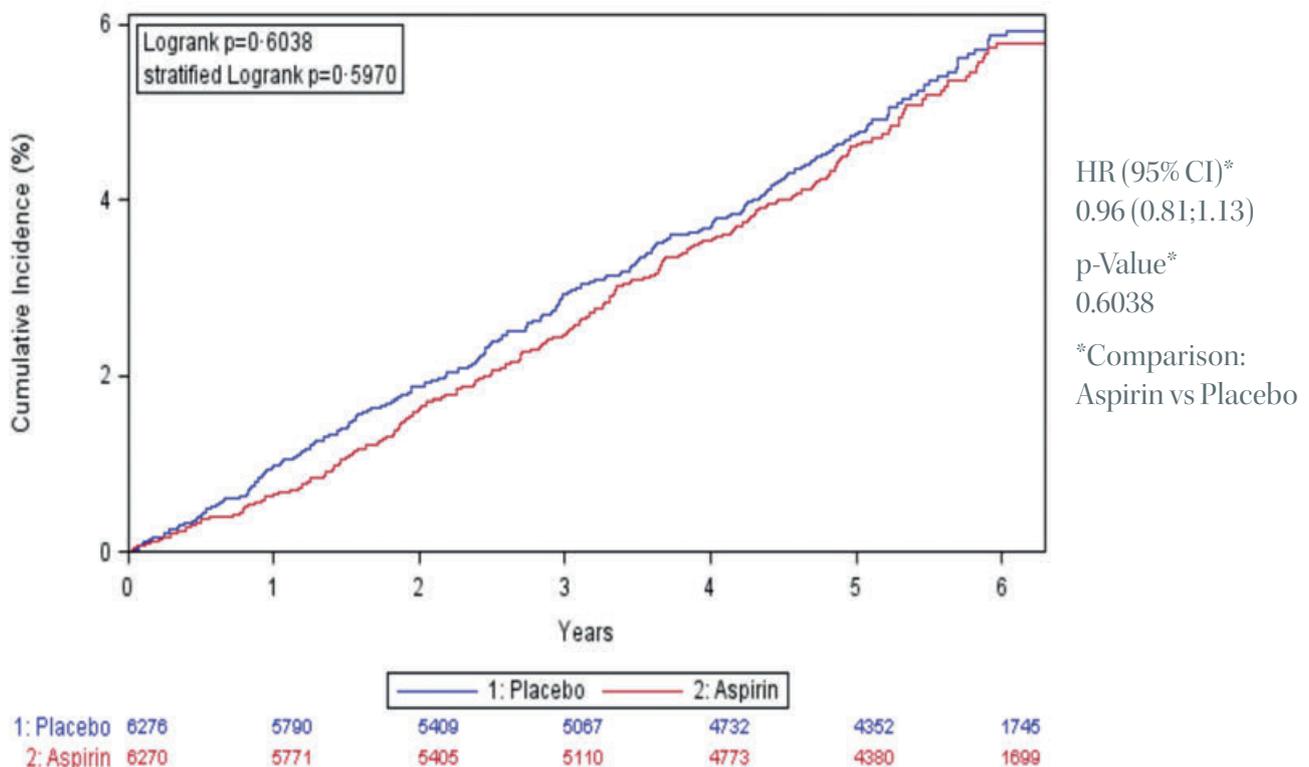
# Aspirin: Trial Updates

## ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events)

This trial, presented on behalf of Professor J Michael Gaziano by Professor Rothwell, recruited 12,546 subjects deemed to be of moderate risk of CVD. This randomised, double-blind, placebo-controlled, multicentre study assessed the effect of 100 mg enteric-coated aspirin daily versus placebo in men 55 years and older with 2 or more CVD risk factors and women 60 years and older with 3 or more CVD risk factors. The demographic figures for the study show a mean elevated BMI in the participants as would be expected for a group with a moderately increased overall level of CVD risk. The primary efficacy endpoints were time to first occurrence of CVD death, myocardial infarction (MI), unstable angina (UA) and transient ischemic attack (TIA). Safety end points included bleeding events and incidence of adverse events. Protocol amendments (e.g. including UA and TIA) and extended treatment and follow up were made during the study after a lower than expected event rate was found. This resulted in 60,000-person years of data being achieved.

### Primary Efficacy Endpoint: CVD Death, MI, UA, Stroke or TIA

Time to First Occurrence of CV Death, MI, UA, Stroke or TIA (Intent-to-Treat population)



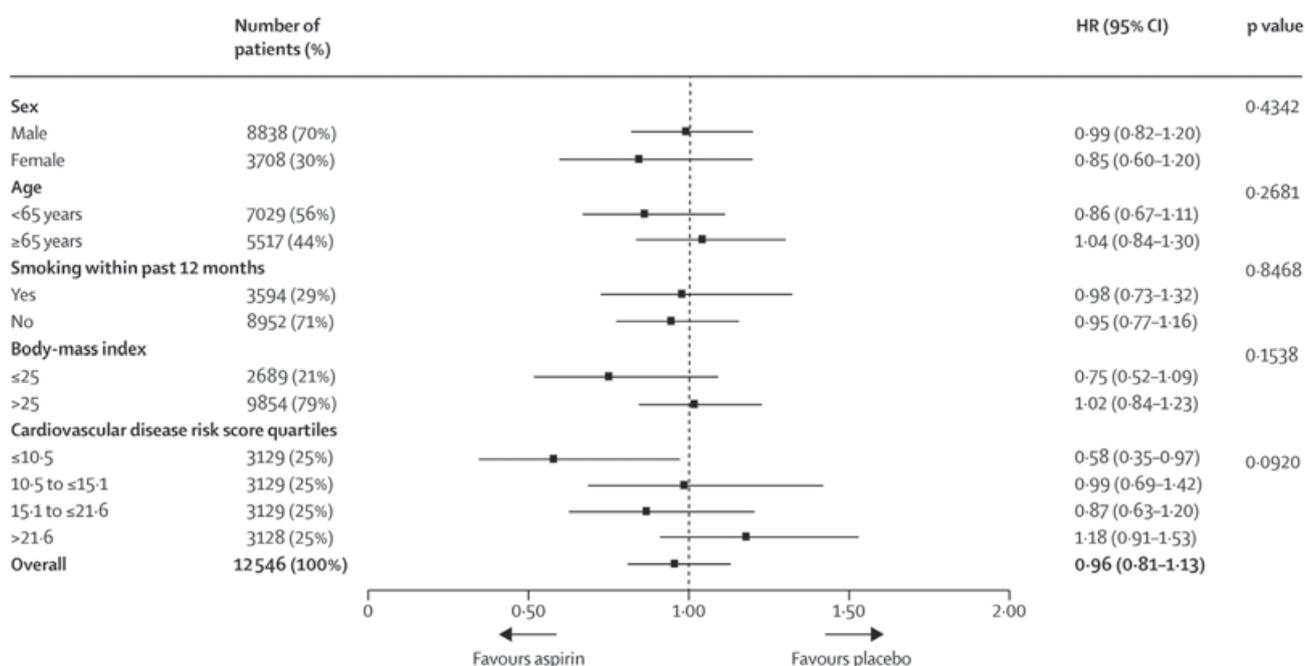
*The Lancet*, S0140-6736(18)31924-X, Gaziano et al, Reprinted from Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial, Copyright (2018), with permission from Elsevier

The trial's aim of assessing the role of aspirin in the primary prevention of CVD, in patients at moderate risk, was complicated by a much lower than anticipated event rate. This reflects better overall management of CVD risk factors in the general population with, for example, strict cholesterol and blood pressure control and smoking cessation. ARRIVE found no overall reduction in major CVD events in the intent to treat population. However, the risk of first MI in those who were at least 60% compliant with the study medication (from the per protocol analysis) was lower in the group taking aspirin. Whilst gastrointestinal (GI) bleeding rates were higher in the aspirin treatment group, they were not higher than expected and the rate of severe GI bleeding was extremely low. There was no difference between the two arms in the incidence of fatal events. No reduction in the 5-year risk of cancer was seen in the aspirin arm of the trial but other studies have shown this takes time to emerge.

Some interesting data emerged from the subgroup analysis. Aspirin appeared to perform better in reducing CVD events in those of lower BMI and CVD risk. This does reflect the analysis of previous studies.

## Time to first occurrence of CV Death, MI, UA, Stroke, or TIA by Subgroups

(Intent-to-Treat Population)



*The Lancet, S0140-6736(18)31924-X, Gaziano et al. Reprinted from Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial, Copyright (2018), with permission from Elsevier*

Professor Gaziano, Primary Investigator, concludes;

*“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 benefits against the bleeding risks, patient preferences, cost, and other factors.”*

There was a lot of interest and debate about the ARRIVE trial findings. Adherence over time was discussed and factors influencing this in different countries. Concerns were expressed about looking at the per protocol analysis as the benefits from randomisation are then lost. Different ways to assess these data and their relative merits were debated. The potential for RCTs to underestimate the effects of a drug in the real world were discussed. Overall it was felt that the truth in actual clinical practice may lie somewhere between the actual intent to treat and per protocol analysis.

Many aspirin trials, as with ARRIVE, show that the effect of aspirin diminishes over time. The group discussed whether this was due to a reduction in adherence or if other more complex pathological mechanisms within the body reduce the effect of aspirin with time.

It was agreed that a post-trial follow up of ARRIVE would be very interesting, but this may be complicated by the fact that no consent was gained at the outset for this.

### Reference

*Gaziano JM, Brontons C, Coppolecchia R et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. The Lancet. 2018; 392; 10152: 1036-1046. (ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events).*



ps 69%

# ASCEND

A Study of Cardiovascular Events in Diabetes

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# ASCEND

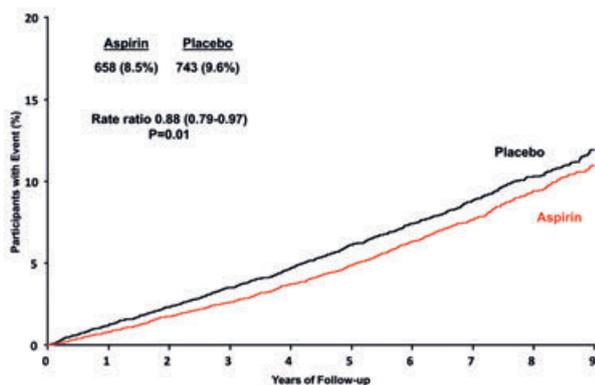
## (A Study of Cardiovascular Events in Diabetics)

Jane Armitage, Professor of Clinical Trials and Epidemiology at Oxford University, presented the ASCEND trial in which 15,480 UK diabetic patients were randomised to receive Aspirin 100mg daily or placebo. (The trial also looked at omega-3 fatty acid supplements versus placebo). The primary outcomes measured were serious vascular and major bleeding events. The trial was carried out by post and online with no study clinics. The mean follow-up period was 7.4 years with some data out to 9 years.

There were 1700 incident cancers in this study but no suggestion that aspirin provided protection against gastrointestinal cancer or other cancer during the average of 7.4 years of follow-up. Whilst aspirin was found to significantly reduce the risk of serious vascular events ( $p=0.01$ ) it also significantly increased the risk of a major bleeding event ( $p=0.003$ ). A major bleed was defined as an event that at least involved being admitted to hospital. This meant the benefit of avoiding a serious vascular event was largely offset by the risk of a major bleed.

The study achieved over 99% completion to follow up, there was a reduction in the adherence rate over time with around 70% average compliance in the aspirin group. Omega-3 fatty acid supplements were found to have no effect on the primary study outcomes. The 1.1% absolute reduction, in the aspirin arm of the study, on the incidence of serious events is modest but given the concern that people with diabetes might not respond to aspirin is an important result.

### Effect of aspirin on Serious Vascular Events



During the question and answer time the fact that many of these patients will have had a high BMI was discussed and whether this may have impacted on the results. Stratifying the results by BMI and by weight was presented and the results did not support the earlier hypothesis that benefit was seen only in those under 70kg. The number needed to treat versus number needed to harm was debated but overall Professor Armitage felt that this was a relatively healthy group of diabetic patients and it is important to be cautious with therapy used in the primary prevention setting. When the risk of CVD is higher the benefit of aspirin to the patient is higher. The possibility of looking at colorectal adenomas as a precursor to colorectal cancer was also discussed.

One of the factors making modern trials more difficult are low event rates due to more aggressive management of risk factors, secular trends and the fact that participants are often not naive to aspirin; in this study 30% of the participants had previous aspirin use. Other drugs can have an effect; Professor Patrignani, mentioned that statins may increase the capacity of aspirin to reach its target COX1 and therefore influence the efficacy of the drug. The many variables within modern day trials may influence how aspirin works. The effect of aging on aspirin use and overall mortality was also discussed but this had not been looked at as a sub group analysis

Watch the trialist commentary here:

<https://www.aspirin-foundation.com/conferences-2018/>

### Reference

The ASCEND Study Collaborative Group. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *NEJM* 2018 DOI: 10.1056/NEJMoa1804988 (ASCEND = A Study of Cardiovascular Events in Diabetes).



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# ASPREE

## (ASPirin in Reducing Events in the Elderly)

Professor John McNeil presented his data for the first time taking the audience through the results from the ASPREE trial in which just over 19,000, community-dwelling men and women, age 70 years plus in Australia and the US or 65 years or more in US minority groups, were included in a randomised, double-blind, placebo-controlled trial to measure the effect of 100 mg enteric coated aspirin on disability-free survival. The trial involved a lot of intensive follow-up, participants were seen yearly and phoned every 3 months. Radio publicity was also used to increase participation

Disability-free survival was chosen as the primary endpoint because this is in essence the fundamental reason why a medication is used, and it integrates both the benefits and harm from aspirin use. Secondary endpoints included all-cause mortality, incident dementia, persistent physical disability, fatal and non-fatal CVD, fatal and non-fatal cancer, mild cognitive impairment, depression and major haemorrhage.

Only participants with 80% or more adherence during a month's placebo run in were randomised to receive either aspirin or placebo during the study.

### Composite Primary End Point, Including the Components, and Secondary End Points of Death, Dementia, Persistent Physical Disability and Major Hemorrhage\*.

	Aspirin		Placebo		Aspirin v. Placebo		
	N = 9525		N = 9589		Hazard ratio	95% CI	P-value
	No. events	Rate per 1000 PY	No. events	Rate per 1000 PY			
Primary end point†	921	21.5	914	21.2	1.01	0.92-1.11	0.79
Death from any cause	480	11.2	431	10.0			
Incident dementia	274	6.4	275	6.4			
Persistent physical disability	167	3.9	208	4.8			
Secondary end points‡							
Death from any cause	558	12.7	494	11.1	1.14	1.01-1.29	
Dementia	283	6.7	292	6.9	0.98	0.83-1.15	
Persistent physical disability	188	4.9	224	5.8	0.85	0.70-1.03	
Major hemorrhagic events	361	8.6	265	6.2	1.39	1.18-1.62	<0.001
Clinically significant bleeding	312	7.4	225	5.3			
Hemorrhagic stroke	49	1.2	40	0.9			

\* The 95% confidence intervals and P values were not adjusted for multiple comparisons.

† The primary end point was the first occurrence of any one of the three components (death from any cause, dementia or persistent physical disability).

‡ For the secondary end points, all the participants who had an event at any time during the trial are counted. Other secondary end points included fatal and nonfatal cardiovascular disease, fatal and nonfatal cancer, mild cognitive impairment, and depression.

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The trial was stopped at a median of 4.7 years follow-up after it became clear that taking aspirin for primary disease prevention, over 70 years of age, had no effect on disability free survival. At this point the rates of CVD (as defined by fatal coronary heart disease, nonfatal myocardial infarction and nonfatal stroke and hospitalisation for heart failure) were 10.7 and 11.3 events per 1000 person-years in aspirin and placebo groups respectively [Hazard ratio 0.95, 95% CI 0.83 to 1.08]. Major haemorrhage (as defined by haemorrhagic stroke, symptomatic intracranial bleeding or clinically significant extracranial bleeding) was seen at a rate of 8.6 and 6.2 events per 1000 person-years in aspirin and placebo groups respectively [Hazard 1.38, 95% CI 1.18 to 1.62, P<0.001]. No benefit was seen in terms of cancer outcomes, but the trial was stopped at 4.7 years which maybe too early to see this with aspirin.

During the question and answer session the many observational studies supporting aspirin use to reduce cancer incidence were discussed and how these studies showed clear heterogeneity in support of aspirin. It was agreed that long term follow up of the ASPREE study participants would be of interest to see if there is a latent effect on cancer incidence. It may however be possible that cancer biology changes with age and therefore a benefit with aspirin is not evident. Another reason for the results debated by the oncologists in the audience is whether the trial medication was stopped if they were diagnosed with cancer and if aspirin was previously helping to control a cancer that then grew more quickly. The pharmacologists commented that mechanistic studies to better understand what is happening inside the platelets will help with the interpretation of the clinical trial results.

This study raises concern about the use of low-dose aspirin for the primary prevention of cardiovascular disease (CVD) after age 70 due to changes in the body that result from aging. Best practice on how to safely terminate aspirin in a way that avoids a bounce back effect on the person's platelets resulting in increased blood clotting and CVD risk needs to be established and further research in this area will be beneficial. Using aspirin for the secondary prevention of CVD was clearly viewed as different as here the risk of another CVD event is higher and is this capacity aspirin can be used past age 70. The evidence so far suggests using aspirin in a younger (50-69 years) age group for the primary prevention of CVD and cancer is useful as this population will then have less CVD events and appear also to experience a long-term reduction in cancer incidence with less overall adverse drug events than an older population.

**Watch the trialist commentary here:**

<https://www.aspirin-foundation.com/conferences-2018/>

## References

McNeil JJ, Woods RL and Nelson MR et al. *Effect of Aspirin on Disability-free Survival in the Healthy Elderly.* NEJM. 2018 DOI:10.1056/NEJMoa1800722 (ASPREE = ASPirin in Reducing Events in the Elderly).

McNeil JJ, Nelson MR and Woods RL et al. *Effects of Aspirin on All-Cause Mortality in the Healthy Elderly.* NEJM. 2018 DOI: 10.1056/NEJMoa1803955 (ASPREE).

McNeil JJ, Wolfe R and Woods RL et al. *Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly.* NEJM 2018 DOI: 10.1056/NEJMoa1805819 (ASPREE).





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KNOWLEDGE MADE USEFUL

Professor James Jardine



# AspECT

## (Aspirin and Esomeprazole Chemoprevention Trial)

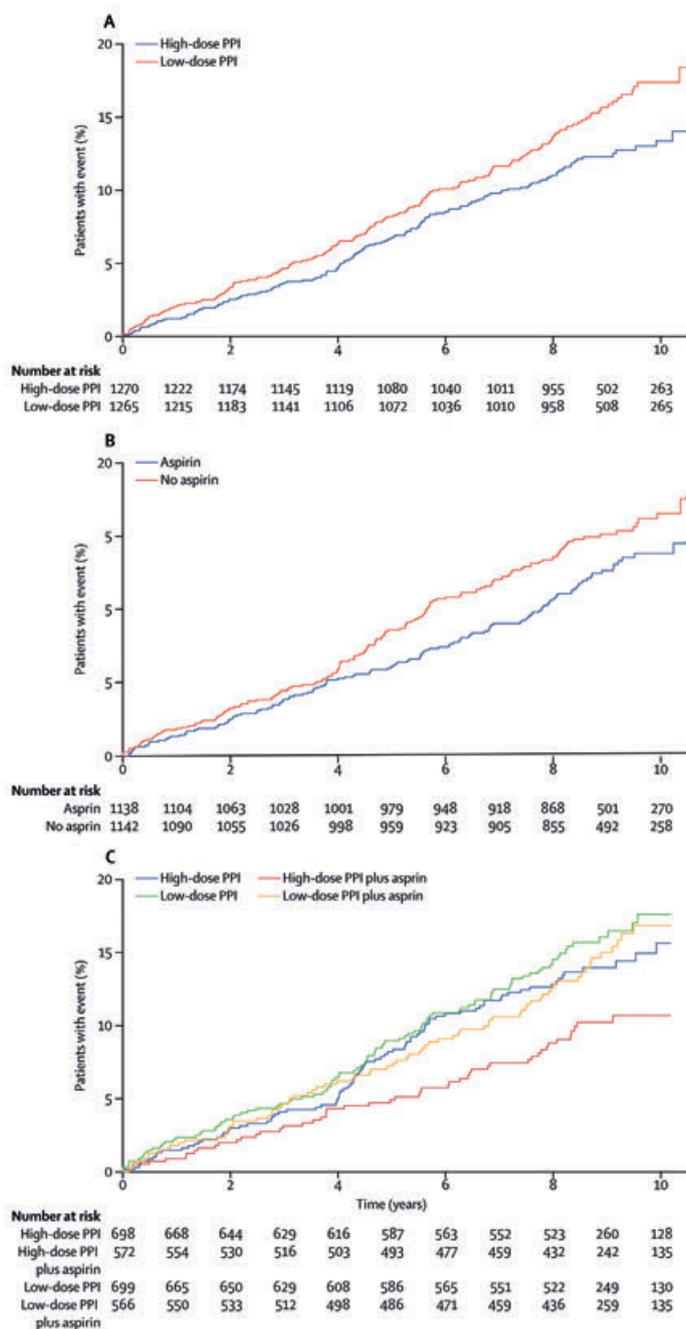
The AspECT, a phase III randomised study in Barrett's metaplasia (Aspirin and Esomeprazole Chemoprevention Trial) presented by principal investigator, Professor Janusz Jankowski looked at the effect of aspirin and/or a proton pump inhibitor (PPI) to reduce the incidence of oesophageal adenocarcinoma in high risk groups. The theory behind this is that using a PPI reduces acid reflux and aspirin reduces inflammation and therefore both strategies have potential chemo preventative properties for reducing the incidence of oesophageal adenocarcinoma. This is really important as the 5-year survival with this cancer is currently only 10%.

This was a 2x2 factorial study, a no PPI arm was not allowed as the funders felt this would be disadvantageous to patients and there was no placebo control as this would make the cost of the study prohibitive. Instead there was high (80mg daily) or low dose (20 mg daily) PPI and aspirin or no aspirin arms. The study had a power of 80%, 2,500 patients were recruited, and 196 events occurred during 20,000 patient-years of follow-up. The composite endpoints were time to high grade dysplasia, adenocarcinoma and death. 55% completed the entire study on the originally randomised medications at 9 years and of those randomised 99.3% were included in the final Intent to Treat (ITT) analysis and active follow up. Through rigorous processes 100% of the serious adverse events were collected and investigated.

The basic demographics of the study showed that the study population were of reasonably high risk and the majority had at least 3 cm of Barrett's oesophagus. It is understood that the bigger the premalignant lesion the higher the risk of oesophageal cancer. This is due to the increase in stem cells caused by the damage to the oesophagus.

The results showed that high dose PPI was more effective than low dose PPI and that aspirin use was beneficial; both results had borderline (5%) statistical evidence. The strongest evidence for PPI use was seen in all-cause mortality and the strongest evidence for aspirin as a chemo preventative was seen for high grade dysplasia, especially when patients who received non-steroidal anti-inflammatory (NSAIDs) were removed from the analysis. The SAEs were similar in both primary comparisons and the combination of aspirin and a PPI worked well with less than 1% serious adverse events. The use of a high dose PPI may have been helping patients to benefit from aspirin without experiencing the gastrointestinal bleeding issues. Overall high dose PPI plus aspirin showed the best results. Although adding aspirin to the PPI just missed statistical significance, this became statistically significant if the findings were censored for prior NSAID use.

# Aspirin: Trial Updates and Science Awards 2018



Total Events = 313  
Events needed = 196

*The Lancet, S0140-6736(18)31388-6, Jankowski et al, Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial, with permission from Elsevier*

Professor Jankowski presented the clinical impact of this study. The number needed to treat (NNT) for PPI and aspirin is 1 in 30, the NNT from aspirin alone is 1 in 43. From a health economic point of view the cost is around £3,000-£10,000 well within the £30,000 QUALY cut off. The impact of this work will be to decrease the incidence of deaths in a disease with poor diagnosis and prognosis and the program itself is likely to be delivered largely by general practice teams.

Watch the trialist commentary here:

<https://www.aspirin-foundation.com/conferences-2018/>

## Reference

Jankowski JAZ, de Caestecker J, Love SB et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. 2018 *The Lancet*; 392:10145:400-408. (AspECT = Aspirin and Esomeprazole Chemoprevention Trial).

# seAFood

## (Systematic Evaluation of Aspirin & Fish Oil)

Professor Mark Hull gave an overview of the findings from the seAFood (Systematic Evaluation of Aspirin and Fish Oil) colorectal polyp prevention trial the details of which will be included in a downloadable PDF as soon as the trial is published. This is an important study because there is currently an unmet need for improved CRC prevention, with interval cancers occurring despite bowel screening programmes.

**In the meantime, the trialist commentary can be watched here:**

<https://www.aspirin-foundation.com/conferences-2018/>



# Aspirin: Trial Updates and Science Awards 2018

## connections, debate, questions and clarity

Overall, the meeting raised much debate and clearly there is more complexity to aspirin's mechanism of action within the body than first understood. A multitude of factors connected with the dose of aspirin used and the human body it goes into has an influence on what takes place at a cellular level. The pharmacologists at the meeting, including the Senior Science Award Winner Professor Paola Patrignani, added to the discussion by helping to put the new clinical findings into the context of what is known about the mechanism of action of aspirin and drew attention to the many factors that can influence its pharmacokinetics and pharmacodynamics in humans.

The International Aspirin Foundation has a unique ability to facilitate high level discussion of aspirin by experts at a global level. The work discussed at this meeting ranged from pharmacology, aspirin primary prevention, aspirin in the elderly and aspirin for cancer prevention. The energetic and enthusiastic sharing of ideas and debate amongst a very distinguished international audience added immensely to the quality of the event. The level of interest stimulated at the meeting, in which five new aspirin trials were presented and the aspirin research from two highly successful scientists celebrated, demonstrates that the future is exciting for this 121-year-old medicine. Further discussion and debate will continue as researchers strive to build the knowledge that is vital for enabling the clinician and patient to have a well-informed discussion, therefore ensuring the right populations of patients continue to benefit from aspirin.



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Emerging Aspirin Investigator Award kindly supported by G L Pharma

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