



# Aspirin Disease Prevention and Current Research Summaries

The purpose of this report is to provide a relatively concise and current overview of activity, which reflects the depth of expertise and knowledge of the members of the Scientific Advisory Board, from both geographical and scientific areas. This shared information enables The International Aspirin Foundation to provide educational material for medical professionals. It is not meant to be an exhaustive amount of information, rather what the experts regard as the most relevant and topical activity to comment upon.

The topics the Scientific Advisory Board considered in their summaries are:

- Primary disease prevention using aspirin
- Secondary disease prevention using aspirin
- Other new trials or recently published science of interest about aspirin
- New or existing research on aspirin in their geographical locality
- Relevant conferences or meetings in their geographical locality or scientific area concerning aspirin
- References of interest for further information



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## Short-term effect of aspirin after TIA and minor stroke

The risk of major stroke is up to 10% in the days after a transient ischaemic attack (TIA) or minor stroke without appropriate treatment. Urgent medical treatment appears to reduce that risk by as much as 80%, but many patients delay seeking medical attention. In a recent population-based study in the UK, half of recurrent strokes in the days after a TIA occurred prior to medical attention being sought for the initial event.

Antithrombotic treatment is important in the immediate management of most acute ischaemic vascular events. Since aspirin is available in many households public education materials recommend self-administration by patients who develop acute chest pain, in addition to seeking immediate medical attention. There are, however, few published data from randomised trials on the effect of aspirin on risk of early recurrent stroke after TIA and minor stroke, and no data on severity. Randomised trials of aspirin vs. placebo in longer-term secondary prevention showed only a 13% relative reduction in risk of recurrent stroke. Trials of short-term treatment of hospitalised acute stroke also reported a 13% reduction in the 4 week risk of recurrent stroke or intracerebral haemorrhage, but the effect of aspirin on risk or severity of recurrence after more minor stroke was not reported.

In the absence of published randomised evidence of the effect of aspirin on risk and severity of early recurrent stroke after TIA and minor stroke, researchers re-analysed individual patient data and reviewed original paper records on early outcomes from all available trials of aspirin vs. placebo in secondary prevention after TIA or ischaemic stroke. To more reliably estimate the very early time-course of onset of effects of aspirin, they also studied risk of recurrent ischaemic stroke in trials of aspirin in treatment of acute stroke, stratified by severity of the pre-randomisation neurological deficit.

Among 15,778 patients in 12 trials of aspirin vs. control in secondary prevention, aspirin reduced the 6-week risk of major ischaemic vascular events by 70-80% (disabling or fatal ischaemic stroke - HR=0.29, 0.20-0.43, p<0.0001; acute myocardial infarction - HR=0.22, 0.09-0.53, p=0.0008), with greatest benefit in patients with TIA or minor stroke (disabling or fatal ischaemic stroke: 0-2 weeks-HR=0.07, 0.02-0.31, p=0.0004; 0-6 weeks-HR=0.19, 0.11-0.34, p<0.0001). The effect of aspirin on early recurrent ischaemic stroke was due partly to a substantial reduction in severity (mRS shift analysis: OR=0.43, 0.26-0.72, p=0.001). Some further reduction in risk of ischaemic stroke on aspirin vs control accrued from 6-12 weeks, but benefit after 12-weeks was limited (stroke risk-OR=0.97, 0.84-1.12, p=0.67; severity-mRS 'shift' OR=1.00, 0.77-1.29, p=0.97). In trials of aspirin versus control in major acute stroke (40,531 participants in 3 trials), the reduction in risk of recurrent ischaemic stroke was most evident in patients with less severe baseline deficits (interaction-p=0.014), and was substantial by the second day after starting treatment (2-3 days-HR=0.37, 0.25-0.57, p<0.0001).

The findings confirm that medical treatment substantially reduces the risk of early recurrent stroke after TIA and minor stroke and identify aspirin as the key intervention. The considerable early benefit from aspirin warrants public education about self-administration after possible TIA. The previously unrecognised effect of aspirin on severity of early recurrent stroke also has implications for understanding mechanisms of action.

## References

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## Primary disease prevention using aspirin

In 2007, the U.S. Preventive Services Task Force (USPSTF) recommended against the use of aspirin for the prevention of colorectal cancer (CRC), but in April 2016, it published new guidelines which reversed this position. Supporting evidence had become compelling enough to include CRC prevention into their rationale for routine low-dose aspirin use among certain subgroups of adults with specific cardiovascular risk profiles.

This recommendation distinguishes aspirin as the first pharmacologic agent that the USPSTF has endorsed for chemoprevention of a cancer in a population not characterized as high risk. However, both the USPSTF and a UK panel have emphasized the need for additional research into the effect of long-term aspirin use on not only the incidence of CRC, but also of overall cancer, according to a range of doses and by subgroups, including age, sex, baseline cancer risk, or comorbid conditions. It is also unclear what the additional impact of aspirin use on cancer would be in the setting of screening, including lower endoscopy, which is associated with a significantly lower risk of CRC.

To address these critical questions, we examined the association of aspirin with incident cancer among 135,965 women and men enrolled in two large prospective U.S. cohort studies who provided detailed and updated information on aspirin use. In up to 32 years of follow-up, we documented 20,414 cancers among women and 7,571 among men. Compared with non-regular use, regular aspirin use was associated with a lower risk of overall cancer (RR 0.97; 95% CI 0.94, 0.99), which was primarily due to a lower incidence of gastrointestinal cancers (RR 0.85; 95% CI 0.80, 0.91), especially colorectal cancers (RR 0.81; 95% CI 0.75, 0.88). The benefit of aspirin on gastrointestinal cancers appeared evident with use of at least 0.5 to 1.5 standard aspirin tablets per week; the minimum duration of regular use associated with lower risk was 6 years.

In people over 50 years old, regular aspirin use could prevent 33 colorectal cancers (PAR 17.0%) in those who have not had a lower endoscopy and 18 colorectal cancers per 100,000 person-years (PAR 8.5%) in those who have.

In conclusion, regular use of low doses of aspirin for at least 6 years was associated with significantly lower risk of overall cancer, primarily gastrointestinal tumours. Although aspirin may prevent colorectal cancers irrespective of screening, substantially more cases appear to be prevented among those who do not undergo screening.

*These data are in press at JAMA Oncology*

## Recently published science of interest about aspirin: aspirin mechanism

In an Opinion article in press at *Nature Reviews Cancer*, we review the weight of the evidence supporting aspirin's chemopreventive potential and highlight advances in our understanding of aspirin's mechanisms of action. We challenge the notion that aspirin prevents cancer through a single, dominant pathway and propose an integrative multi-pathway model for its mode of action. We highlight how these pathways can be leveraged to develop mechanistic biomarkers for personalised risk stratification. Such biomarkers may then be translated clinically in a precision medicine approach critical to the future of aspirin chemoprevention.





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## Science and trial data on aspirin for pain related symptoms in the common cold and flu

My area of interest is in studying the symptoms of acute upper respiratory tract infections such as common cold and flu, especially the mechanisms that cause the symptoms, and how they may be alleviated by treatments such as pain killers like aspirin. My interest in aspirin is as a treatment for pain-related symptoms of common cold and flu such as fever, sore throat pain, headache, muscle aches and pains and sore throat.

## Pharmacology of aspirin as an analgesic for acute pain.

Aspirin works as a pain killer by inhibiting the enzymes that produce prostaglandins. This was discovered in the 1970's and led to a Nobel Prize for Sir John Vane. Since then there have been great advances in understanding the pharmacology of aspirin and how it works in other diseases such as cardiovascular disease and cancer. Its efficacy as an analgesic has been shown in many clinical trials on acute pain such as headache and migraine, common cold and flu, muscle aches and pains, menstrual pain, toothache and pain after tooth extraction, and minor aches and pains of arthritis<sup>1</sup>. Randomised, placebo controlled clinical trials have been conducted in all these pain conditions and they now provide hard clinical evidence for the efficacy of aspirin as an analgesic.

To study the efficacy of analgesics we need a patient pain model that is relatively predictable and standardised. The pain of removal of impacted third molars is useful for clinical trials because it is a common dental procedure and its timing and intensity of the pain are predictable<sup>2</sup>. Studies on dental pain consistently demonstrate the efficacy of aspirin above placebo and show that aspirin is a more useful analgesic than paracetamol in the control of postoperative pain after third molar surgery<sup>2</sup>.

Aspirin is effective against both migraine and tension-type headache and is recommended as first-line treatment for each of these disorders in various management guidelines<sup>3,4</sup>.

Pain associated with common cold such as sore throat pain is one of the commonest minor pains because of its high incidence throughout the world. Aspirin has been shown to be effective in treating sore throat pain, muscle aches and headache associated with common cold<sup>5</sup>, and in treating fever associated with upper respiratory tract infection<sup>6</sup>.

## Speed of action is important for those who take aspirin as a pain killer.

Patients with acute pain demand an analgesic providing rapid relief of pain. Aspirin tablet studies have shown that their formulation has marked effects on its absorption and pharmacokinetics. Simple aspirin tablets have the slowest absorption into the blood stream and the speed of absorption can be greatly increased by giving aspirin as an effervescent formulation, and be further speeded up by buffering the aspirin<sup>7,8</sup>. The time to peak plasma concentration of aspirin in tablet form varies between 33-83 minutes, and recently its rate of absorption has been greatly accelerated by using micronized tablets with an effervescent nucleus, reducing absorption time to only 18 minutes<sup>4</sup>.

## A future super aspirin?

In future the pain-killing action of aspirin may be increased by modifying its formula. Attaching nitric oxide and hydrogen sulphide donors to the aspirin molecule may enhance its analgesic efficacy<sup>9</sup>. This is an interesting development that opens up a new field of research on aspirin as an analgesic and anti-inflammatory medicine.

The development of nitric oxide (NO)- and hydrogen sulphide (H<sub>2</sub>S)-releasing nonsteroidal anti-inflammatory drugs (NSAIDs) has generated more potent medicines with increased safety profiles. The painkilling (antinociceptive) activity of a new hybrid molecule incorporating both NO and H<sub>2</sub>S donors into aspirin (NOSH-aspirin) has been compared with aspirin in different models of inflammatory pain. The results suggest that NOSH-aspirin represents a prototype of a new class of analgesic drugs with more potent effects than the traditional NSAID, aspirin.

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# The Risks and Benefits of Aspirin in the Primary Prevention of Cardiovascular Disease and Cancer

The benefits of aspirin in the secondary prevention of cardiovascular disease (CVD) have been conclusively demonstrated in hundreds of randomized trials those benefits clearly outweigh the risk for most patients. The risk-benefit analysis is more complicated for those who do not have known cardiovascular disease (CVD), and the data come from a smaller number of primary prevention trials. The US Preventive Services Task Force (USPSTF) recently released recommendations for the use of aspirin taking into account the potential value of aspirin in lowering the risk of CVD and colorectal cancer (CRC) and the potential risk of bleeding <sup>(1,2)</sup> updating recommendations from 2009 <sup>(3)</sup>.

The summary recommendations suggest the use of aspirin for those age 50-59 with a 10-year CVD risk of greater or equal to 10% as a Grade B recommendation and that the recommendation for those 60-69 years should be individualized with a Grade C recommendation. Specifically, persons aged 60-69 years who are not at increased risk for bleeding, have a 10-year life expectancy and are willing to take daily low dose aspirin for 10 years are more likely to have a net benefit. For those below 50 and 70 years and above, the data were insufficient for a firm recommendation.

These summary recommendations were based on a sophisticated decision analysis on the role of aspirin in primary prevention <sup>(4)</sup> and a series of additional supporting analyses carried out on behalf of the USPSTF <sup>(5-10)</sup>. Previously, the USPSTF issued guidelines on the use of aspirin in the primary prevention of vascular events <sup>(3)</sup> were based only on cardiovascular benefit and bleeding risk. The 2016 recommendations consider not only the cardiovascular event reduction and risk of bleeding, but also considers newer data on the benefits of aspirin in the prevention of colorectal cancer that is apparent over a longer time frame than the CVD benefit.

The decision analysis relied on, among other sources, the recent systemic reviews done on behalf of USPSTF (5-9) exploring the specific risk and benefits of aspirin on CVD, cancer and specifically colorectal cancer (CRC), all-cause mortality, and bleeding risks. The authors used a CVD simulation model adding CRC incidence and fatality. The model was applied separately to men and women in various age strata. The authors considered lifetime risks as the primary time horizon but also consider 10 and 20 year time window. They found a net benefit lifetime improvement in quality adjusted life years (QALYs) for most groups of men and women age 40 to 69 years, but no such overall benefit for those 70 to 79. The benefit was also present for total life-years for most but not all groups of men and women 40 to 69 years.

These analyses and the subsequent recommendations make it clear that there are subpopulations where there appears to be an overall net benefit of low dose aspirin for the primary prevention of CVD events and CRC. These recommendations are among the first to carefully consider long-term impact of low dose aspirin on cancer risk, in particular colorectal cancer risk. Since this risk-benefit assessment is complex, it makes sense to consult a physician when considering the use of aspirin in primary prevention for a specific person.

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# Secondary disease prevention using aspirin in the treatment of cancer

## Background:

Pre-clinical, epidemiological and randomised data suggest that aspirin could prevent or delay the spread and development of cancer, particularly secondary cancers (metastases) <sup>(1)</sup>.

The observation that taking aspirin after a cancer diagnosis is associated with improved cancer-specific and overall survival has led to clinical trials evaluating aspirin as a treatment for cancer (particularly as an adjuvant to other treatments) and to the search for biomarkers predicting response. A major part of the evidence base relating to aspirin and cancer has come from randomized trials designed to evaluate the vascular effects of aspirin <sup>(2-5)</sup>.

Rothwell *et al.* analyzed data from 51 randomised trials, with ~77,000 participants. There were 19% fewer cancers (hazard ratio 0.81 [95% CI 0.7-0.93]) among those that took aspirin for 5 years or more. There was also a 15% reduction in cancer deaths in tumours arising from different sites including the gastrointestinal tract, breast, prostate and lung.

The most relevant observation for treatment of cancer was that within a few years of starting aspirin there were beneficial effects on cancer outcomes. The cancers that did develop when these trial subjects were taking aspirin were subsequently found to be less likely to have spread (or have formed metastasis) at diagnosis and were less likely to do so later.

## Possible mechanisms of action for aspirin's effect on cancer:

A once daily dose of 75 to 300mg aspirin has a half-life of ~ 20 minutes and the primary target is thought to be Cox-1 activity in platelets. Platelets have been implicated in the spread and the development of metastases. Platelets may also be involved in the development of primary tumours through growth factors and other paracrine signaling pathways. There is an inconsistent reported relationship between tumour Cox-2 expression and aspirin benefit. Other target biomarkers include PIK3CA expression in tumours, which has been studied in four different studies (Table 1) <sup>(6)</sup>, and Human Leukocyte Antigen (HLA) expression on tumour cells (Table 2) <sup>(7)</sup>.

Table 1 Studies examining PIK3CA mutation, aspirin use and colorectal cancer outcomes.

Study	% PIK3CA Mutant	End-point	PIK3CA Mutant			PIK3CA Wild-Type		
			No aspirin	Aspirin	HR (p value)	No aspirin	Aspirin	HR (p value)
Nurses' Health Study ft Health Professionals Follow-up Study (Liao 2012)	16.7%	OS	95	66	0.54 (0.01)	466	337	0.94 (0.96)
		CSS	-	-	0.18 (<0.001)	-	-	0.96 (0.76)
VICTOR trial (Domingo 2013)	11.6%	OS	90	14	0.29 (0.19)	681	111	0.95 (0.26)
		RFS	-	-	0.11 (0.027)	-	-	0.94 (0.79)
Moffitt Cancer Centre & Royal Melbourne Hospital (Kothari 2015)	12.4%	OS	136	49	0.96 (0.86)	-	-	-
		CSS	-	-	0.60 (0.14)	-	-	-
Eindhoven Cancer Registry (Reimen 2014)	15.8%	OS	73	27	0.73* (0.4)	348	147	0.55 (<0.001)

\* =Adjusted rate ratio, OS=overall survival, CSS=colorectal cancer specific survival, RFS=recurrence free survival, HR=multivariate hazard ratio

## Human Leukocyte Antigen (HLA) data:

Platelets are thought to protect disseminating tumour from attack by natural killer cells, which recognize and eliminate cells with low/absent expression of HLA class I antigen. It was proposed that the survival benefit associated with low-dose aspirin use after a cancer diagnosis would be associated with tumours that have low or absent HLA class I antigen expression. However, this study appeared to show the reverse <sup>(7)</sup>.

Table 2 HLA data

Characteristic	No. of Patients	No. of Deaths	Univariate RR (95% CI)	P Value <sup>b</sup>	Adjusted RR (95% Ci) <sup>c</sup>	P Value <sup>b</sup>
HLA class I antigen						
Loss						
No aspirin use	263	123	1 (Reference)	.74	1 (Reference)	.91
Aspirin use	57	26	1.08 (0.70-1.64)		1.03 (0.66-1.61)	
Expression						
No aspirin use	521	257	1 (Reference)	.003	1 (Reference)	<.001
Aspirin use	122	42	0.61 (0.44-0.85)		0.53 (0.38-0.74)	

An alternative hypothesis is that HLA expression is needed for NFκb-mediated platelet signalling which promotes epithelial-mesenchyme transition and enhanced metastatic potential which aspirin inhibits.

## Summary

- There is increasing evidence that aspirin has anti-cancer effects (possibly mediated through platelets).
- A series of large randomised trials are ongoing or planned. They aim to define whether there is a role for aspirin in the treatment of several common tumours.
- These studies will quantify benefits both from an oncology and cardiovascular perspective and any associated risks, in particular the increased risk of bleeding.
- The studies will be long-term projects as the effects on the primary prevention of cancer may take 10-20 years to become apparent.
- Correlative science projects associated with the trials offer the opportunity to understand the anti-cancer mechanisms of aspirin.
- Given the increasing cancer burden in low-resource countries and that aspirin is a low cost generic, potentially these studies could have a large impact on global cancer outcomes if aspirin is shown to be beneficial in the treatment of cancer.

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## Primary cardiovascular disease (CVD) and colorectal cancer (CRC) prevention using aspirin

The US and European guidelines on recommending aspirin for primary prevention have been conflicting, which reflects their uncertainty about the balance of cardiovascular (CV) benefits and bleeding risk<sup>1</sup>. The April 2016 recommendation of the United States Preventive Services Task Force (USPSTF), which includes prevention of colorectal cancer (CRC) among the long-term benefits of aspirin prophylaxis, is likely to have an impact on the next round of treatment guidelines from other organisations.

## Secondary prevention using aspirin

Despite the development and approval of novel antiplatelet agents (e.g., prasugrel, ticagrelor, vorapaxar) during the past 10 years, low-dose aspirin remains the cornerstone of first-line antithrombotic treatment of acute ischemic syndromes (e.g., acute coronary syndromes [ACS]<sup>2</sup>), as well as secondary prevention of their atherothrombotic complications<sup>3</sup>.

The demonstration of additive beneficial effects resulting from effective blockade of the platelet ADP and/or thrombin receptor on top of TXA2 suppression in high-risk patients is consistent with the multifactorial nature of atherothrombosis and the non-redundant nature of these different pathways of platelet activation<sup>4</sup>. However, several randomized trials are underway to determine whether aspirin can be dropped from combined antiplatelet regimens for the long-term management of patients who are treated with one of the new antiplatelet drugs<sup>5</sup>.

Similarly, there are a series of ongoing randomized trials, in which aspirin is being dropped from combined antiplatelet/anticoagulant therapy in patients with atrial fibrillation and ACS or undergoing PCI (see [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). This trend is likely to weaken the place of aspirin in secondary prevention.

## New trials and recently published science of interest on aspirin

A recently published CHEST Guideline<sup>6</sup> addresses the use of low-dose aspirin for the prevention of recurrent venous thromboembolism (VTE): *"In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2C)"*.

## New research on aspirin in Italy

Current clinical trials of aspirin in Italy include ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes), a primary prevention trial coordinated by Dr. Nicolucci at the Mario Negri Institute in Milan, and ASAMET, a randomized, 2x2 biomarker prevention trial of low-dose aspirin and metformin in colon cancer patients coordinated by Dr. De Censi at the E.O. Ospedali Galliera in Genova. Moreover, investigators in Rome, Chieti, Verona, Siena and Bari, coordinated by Prof. Paola Patrignani, are collaborating in investigating the role of platelet activation in intestinal tumorigenesis. They will test the hypothesis that inhibition of platelet activation may explain the efficacy of low-dose aspirin as a chemopreventive agent.

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