

## CANCER PREVENTION WITH ASPIRIN: FACT SHEET

### Summary:

- Over 100 epidemiological/observational studies have reported a significant reduction in cancer among long term regular users of aspirin and other Non-Steroidal Anti-Inflammatory drugs (NSAIDs).
- Meta-analysis of randomised controlled trials using colonic adenomas as an endpoint has revealed a significant reduction in those given aspirin.
- Very long term follow up of participants in early cardiovascular trials revealed a 21% reduction in cancer mortality among those randomised to the aspirin limbs, commencing from 5 years after randomisation.
- Two randomised controlled trials with cancer as a primary endpoint have now reported a significant effect:
  - CAPP2 randomised 1009 carriers of hereditary colorectal cancer (Lynch syndrome due to mutation in a mismatch repair gene) to 600mg aspirin daily for up to four years. Those who complied with the primary aim of treatment for at least 2 years saw a 63% reduction in colorectal cancer and comparable reduction in other cancers associated with the syndrome such as endometrial cancer. The effects became apparent from 4 years after commencing the trial.
  - The Women's Health Study gave alternate day 100 mg aspirin for 10 years to 10,000 American women. There was no effect on cancer at the trial end but subsequent follow up has revealed an 18% reduction in colorectal cancer with the effect becoming apparent after 10 years.
- There is an expert consensus that aspirin should be recommended to those at high risk but ongoing debate about the optimal dose and the risk benefit ratio in the general population.
- CaPP3 will test three different doses 600, 300 and 100mg enteric coated aspirin in 3000 mismatch repair gene defect carriers at risk of Lynch syndrome. All 3000 participants will be receiving aspirin. There is no placebo arm. They will take a blinded dose of 600mg, 300mg or 100mg enteric coated aspirin for two years then receive open label 100mg enteric coated aspirin until the end of the study. Results are expected in 2020. Meanwhile, low dose aspirin can be recommended to any high risk individuals not taking part in the trial.
- Daily aspirin is associated with a 0.1% excess risk of gastric ulcers and gastrointestinal (GI) bleeding. There is a trend to higher risks with higher doses and in old age. The risk is higher in those infected with *Helicobacter pylori*; it is beneficial to exclude/treat infection in anyone commencing aspirin treatment. The risk can be reduced by regular use of a proton pump inhibitor. Occasional blood counts are helpful to detect asymptomatic blood loss.
- There is a 0.01% (1 in 10,000) excess of intracranial haemorrhage per year of use. This risk is offset by reduced thrombotic events in the older population; aspirin side effects are most common in those over 65 years of age and possibly in those with increased blood pressure. The risk of bleeding outside the GI tract is related to platelet inhibition and is not dose related.
- The adverse events are comparable in severity and number to those associated with regular colonoscopy. In 1988, Kune et al<sup>1</sup> demonstrated in a case control study in Melbourne that regular users of non-steroidal anti inflammatories such as aspirin were significantly less likely to develop colorectal cancer. With the exception of one study in elderly Californians, over 100 observational/epidemiological studies since have confirmed this finding with a reduction of around 50% becoming apparent after prolonged use<sup>2</sup>.

A meta-analysis by Cole et al 2009<sup>3</sup> of five adenoma prevention trials supported a protective effect with around 19% fewer adenomas in those prescribed aspirin. The selective COX2 inhibitors had a similar effect<sup>4</sup> but excess cardiovascular events led to cessation of cancer prevention trials.

A series of papers by Rothwell et al<sup>5 6</sup> based on cancer registry data showed a delayed protective effect of the aspirin used in the early cardiovascular prevention trials when compared to the control groups; 674 cancer-related deaths occurred among 25,570 patients. There were 21% fewer deaths from cancer, an effect that began to appear from around 5 years after the original trial had started. The effect did not appear to be dose related. Early trials used up to 1200mg per day, a dose progressively reduced to 75-100mg as it was demonstrated that the anti-platelet effect could be achieved with the smaller safer dose. An alternate day use of 325mg in the US Physicians Health Study Randomised controlled trial did not show an effect on cancer when the data were reanalysed or at long term review<sup>7</sup>. Another RCT, the Women's Health Study used alternate day 100mg aspirin in 39876 women over 45 for a median 10 years and did not show any effect on cancer, one of its primary endpoints. However, long term follow-up, to 18 years in some cases, showed an 18% reduction in colorectal cancers commencing 10 years after the aspirin was started (  $p=0.024$  )<sup>8</sup>.

The only other RCT using cancer as its primary endpoint was **CAPP2** which gave 600mg enteric coated aspirin daily and/or 30 grams of resistant dietary starch to 1009 carriers of a mismatch repair gene defect putting them at risk of Lynch syndrome, formerly known as Hereditary Non-Polyposis colon Cancer or HNPCC. About half of the people with this autosomal dominant disorder develop a solid tumour typically between 35 and 65 years of age. They occur most commonly in the colorectum or endometrium but can affect other parts of the GI tract, kidney, gall bladder, skin, brain etc<sup>9</sup>. The study was designed to run for up to four years with, preferably blinded, follow-up to 10 years. There was no measurable effect on adenoma formation at trial end<sup>10</sup> in either treatment group. At a mean of five years follow up there was still no benefit from resistant starch<sup>11</sup> but a significant effect in those randomised to aspirin<sup>12</sup>. Using a per protocol analysis to focus on those who complied with the primary hypothesis and took aspirin for 2 years, based on tablet counts, there was a greater than 60% reduction (Incident Rate Ratio 0.37 (0.18-0.78)  $p= 0.008$ ) in colorectal cancers and a comparable effect on the overall Lynch syndrome cancer rate. By 2013, there had been 45 new colorectal cancers in the 434 participants who had received placebo but only 25 cancers among the 427 who had received the 600mg aspirin daily.

Given the very high cancer risk among Lynch syndrome carriers, despite regular colonoscopy, all gene carriers should be made aware of this highly significant effect<sup>9</sup>. Steps are being taken to have the anti-cancer effect of aspirin recognised as an indication for routine prescription. In the meantime, there is a need to explore whether the lower doses of aspirin used in cardiovascular prevention are also effective in Lynch syndrome. It may be that Lynch syndrome cancers are more sensitive to aspirin or that the 600mg dose has added benefits. Accepted wisdom is that the 75-100mg dose is only effective against platelets, though it is noteworthy that wild green plants release salicylates to trigger apoptosis (programmed cell death) when infection develops as a form of "scorched earth policy" to limit spread). Our natural diet would have contained measurable amounts of salicylate during our evolution but these are lost in farmed foods, raising the possibility that aspirin is an essential nutrient<sup>13</sup>. A pro-apoptotic effect or enhanced immune surveillance would explain the delayed impact of aspirin use; destruction of damaged stem cells would deplete precancerous cells.

**Our new trial, CaPP3, will explore the differential effects on cancer prevention of aspirin dose.** Lynch syndrome is the result of a loss of function of one of the mismatch repair genes. Three thousand mismatch repair gene carriers will be randomised to receive either 600mg, 300mg or 100mg daily of enteric coated aspirin in a blinded format for 2 years then they will be followed to a minimum of 5 years taking open label 100mg aspirin daily. Using the figures from CAPP2 and comparing all Lynch syndrome cancers rather than just colorectal cancers, this dose non-inferiority trial will have sufficient power to detect a relative benefit of the highest dose of 1.5 i.e. for every three cancers prevented by 600mg per day; there would be at least 2 fewer in the 100mg group.

The need for this trial is driven by popular concern over adverse events even though these are sometimes overstated. In CAPP2, for example, among 861 people treated for up to four years there were 11 significant GI bleeds or ulcers needing hospital treatment in the 600mg aspirin group and 9 in the placebo group, a non-significant excess. This is in keeping with the very large meta-analyses; side effects are most often seen in the elderly. Overall there is a 0.1% excess (1 per 1000 per annum) of clinically significant GI bleeds<sup>14</sup>. The frequency of bleeds is 2 to 3 times higher among those infected with *Helicobacter pylori* and some authorities recommend testing and eradication in anyone contemplating regular aspirin use<sup>15</sup>. Use of a generic proton pump inhibitor offers additional protection at limited cost.

There is a trend to higher rates of bleeding with higher aspirin doses but it should be remembered that the traditional dose used for regular analgesia commenced at 300mg three times daily, making the highest dose in CaPP3 of 600mg a sub-analgesic or “low dose”. Nevertheless, the “high dose” perception will limit routine adoption.

Extra colonic bleeds are the result of the anti platelet effect and are not dose related. The major concern is the 0.01% (1 in 10,000) extra intracranial bleeds. Though rarely fatal, these can be highly debilitating. The protective effect of aspirin against the more common thrombotic stroke offers statistical comfort but disability due to a bleed in an otherwise asymptomatic individual is very distressing. Hypertension is a major factor in haemorrhagic stroke and in the major ATT overview<sup>16</sup> there was a doubling of cerebral haemorrhage for a rise of 20 mmHg in blood pressure (RR 2.18; 95% CI: 1.65, 2.87). In the HOT trial based around use of regular anti-hypertensives and low dose aspirin, there was no evidence of any increase in haemorrhagic strokes associated with aspirin: 19 haemorrhagic strokes (seven fatal) in 9,399 subjects randomised to aspirin and 20 (eight fatal) amongst 9,391 subjects on placebo. Blood pressure monitoring is advisable and active intervention, if there is elevation, appropriate.

There are more than 10,000 adults over 35 in the UK with Lynch syndrome. In the next 10 years about 2000 will develop a cancer despite current surveillance. Allowing for the delayed effect, daily aspirin for the next five years would reduce that number by at least 250. There would be around 50 extra GI bleeds and fewer than 5 intracranial bleeds. Fatality would be exceptional. These high risk individuals will undergo at least 50,000 colonoscopies. Based on the 2011 UK audit<sup>17</sup>, there will be about 125 bleeds requiring transfusion and 20 emergency repairs of perforation. Extrapolating from a recent large scale Canadian study<sup>18</sup>, there could be at least 3 deaths. Thus, the adverse effects and probable benefits of regular aspirin are comparable to current best practice relying on colonoscopy. The results of the CaPP3 trial will help inform this debate and be of relevance in the general population; colorectal cancer is now the second most common and around 1 in 6 sporadic cases share the same molecular mechanism of mismatch repair deficiency as is seen in Lynch syndrome.

**Prepared by Professor Sir John Burn  
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