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Aspirin use after radical cancer therapy – feasibility and toxicity data from the Add-Aspirin trial

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Rationale for the Add-Aspirin Trial

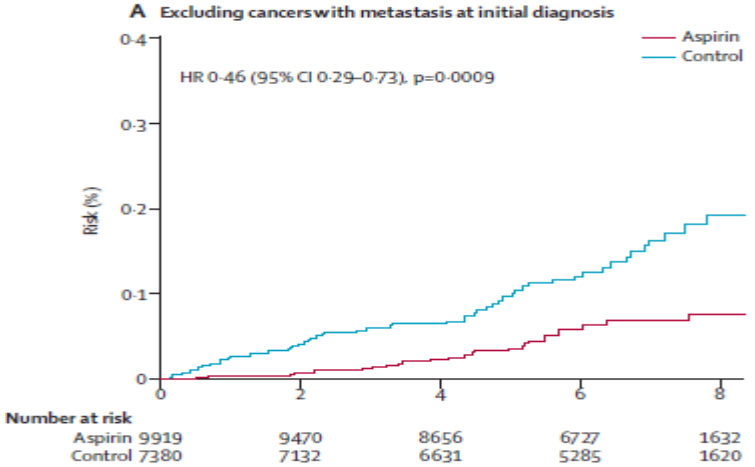
- In vitro, epidemiological and randomised data suggest a possible therapeutic role for aspirin particularly in the adjuvant treatment of several of the most common cancers
- Low cost, generic drug, available worldwide, generally safe with known side effects
- Readily accessible in lower resource settings (unlike many new agents or complex regimens) and therefore the potential for huge global impact

Aim: to assess whether regular aspirin use following primary treatment for an early stage common cancer can prevent recurrence and prolong survival

Randomised Vascular Trials

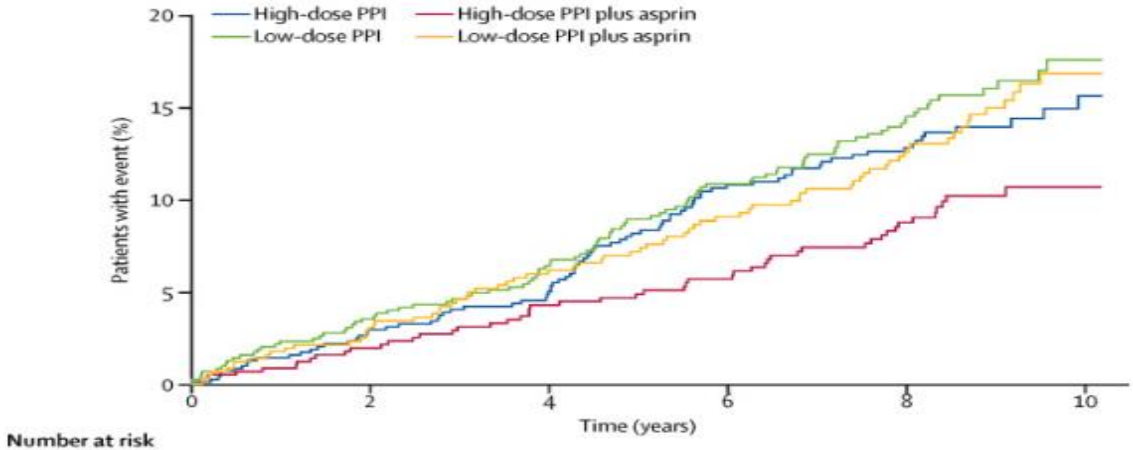
- A major part of the evidence base relating to aspirin & cancer has emerged from RCT's of aspirin in vascular diseases *(Rothwell, Lancet 2010, 2011, 2012)*
- 51 randomised trials with ~77,000 participants
- Decreased cancer incidence HR 0.81 (0.7-0.93) with rx > 5yrs & reduced cancer deaths by ~ 15%

Cancer with no metastasis at presentation in which metastasis developed on follow-up



AspECT Trial:
Esomeprazole and Aspirin in Barrett's Oesophagus

Event Free Survival:



Number at risk											
High-dose PPI	698	668	644	629	616	587	563	552	523	260	128
High-dose PPI plus aspirin	572	554	530	516	503	493	477	459	432	242	135
Low-dose PPI	699	665	650	629	608	586	565	551	522	249	130
Low-dose PPI plus aspirin	566	550	533	512	498	486	471	459	436	259	135

Combination of high dose PPI & aspirin VS low-dose PPI & no aspirin

Time Ratio = 1.59 [95% CI 1.14-2.23], p=0.0068

Only 28/2557 (1%) participants reported study-treatment-related serious adverse events

Jankowski July 2018, The Lancet

Adjuvant Setting: Non-Randomised Data for the Use of Aspirin

Tumour	Study/Year	No of cases	Result (in favour of aspirin)
Colorectal	Bains 2015	25644	CRC-specific mortality: **HR 0.53 (0.50-0.57)** All-cause mortality: **HR 0.71 (0.68-0.75)**
	McCowan 2013	2990	CRC-specific mortality**:** **HR 0.58 (0.45-0.75)** All-cause mortality: **HR 0.67 (0.57-0.79)**
Breast	Holmes 2010	4164	BC mortality: **RR=0.36 (0.24 – 0.65)** Overall Survival: **RR=0.54 (0.41 - 0.70)**
	Fraser 2014	4627	All-cause mortality: **HR=0.53 (0.45 – 0.63)** BC mortality: **HR=0.42 (0.31 – 0.55)**
Gastro-oesophageal	Liu 2009	1716	5 year Overall survival **Aspirin 51.2%, placebo 41%, no tablet 42.3%**
	Staalduinen 2016	560	OS adjusted **RR=0.42 (0.30-0.57)**
	Frouws 2017	1696	OG-specific survival: **HR 0.45 in oesophageal** **HR 0.87 in gastric cancer**
Prostate	Zaorsky 2012	2051	Reduced interval to biochemical failure Aspirin non-use **OR=2.05 (1.33 – 3.17)**
	Choe 2012	5955	PC mortality: **HR=0.43 (0.21 – 0.87)**
	Jacobs 2014	8427	PC mortality: **HR=0.60 (0.37 – 0.97)**

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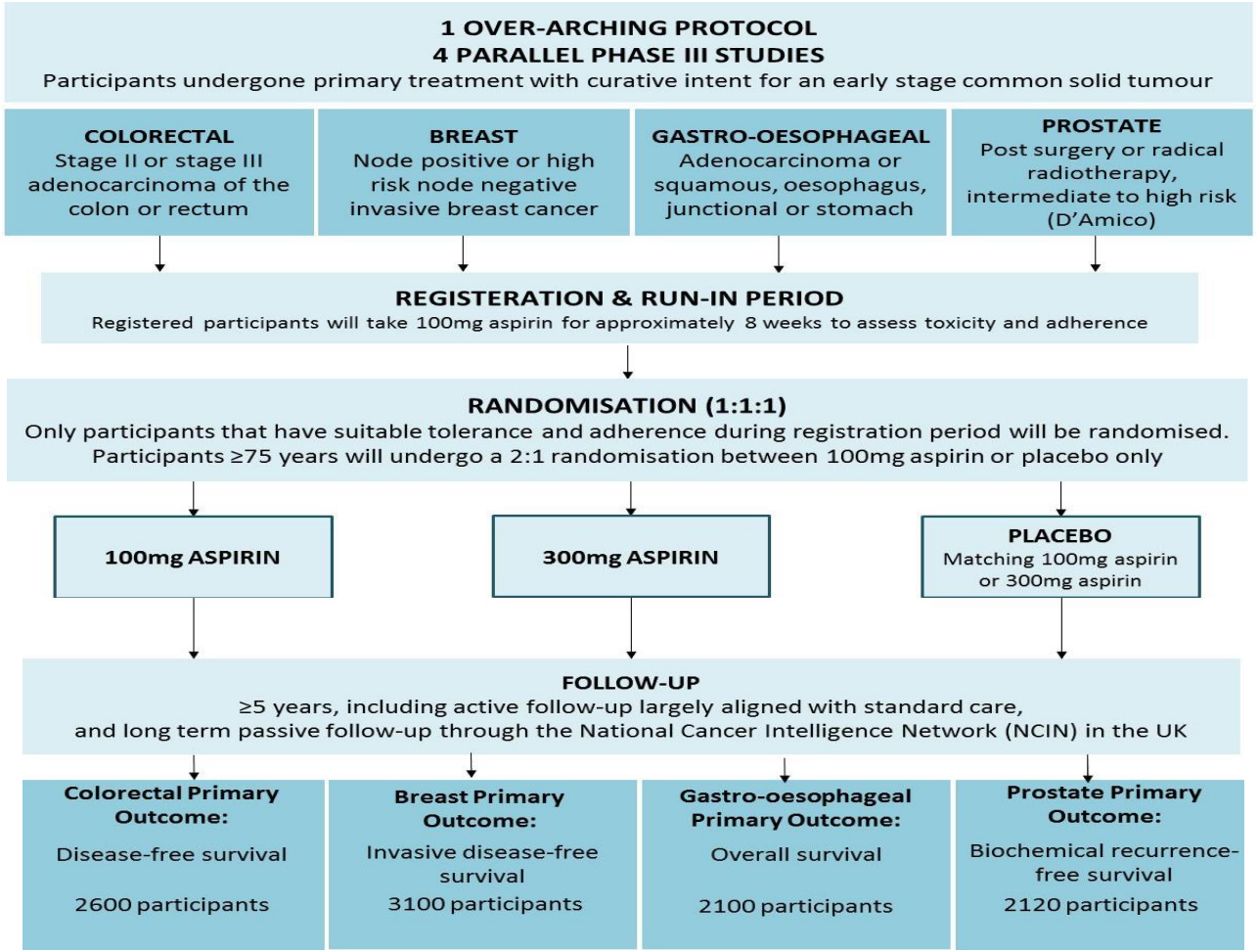
Serious Haemorrhage

Aspirin increases bleeding risk, however this increase is small

Bleeding site	Estimated risk in control group	Estimated risk on aspirin
Serious bleeding** gastrointestinal or other extracranial site	0.07% per year	0.1% per year
Intracranial bleed	0.03% per year	0.04% per year

Antithrombotic Trialists' Collaboration (ATTC) meta-analysis ~95,000 participants, (mean age 56 years, 46% men)
**Serious bleeding = hospital admission or blood transfusion

Trial Design of Add-Aspirin



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Add-Aspirin Feasibility Analysis

- Add-Aspirin opened October 2015
- Pre-planned feasibility analysis after 2 years based on data from the run-in period
  - Adherence, tolerability and randomisation rates
- n=3494 registered across tumour groups

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Adherence and Toxicity

(Data from the run-in period, n=2253, all tumour groups)

- Adherence generally very good across all tumour groups – 2148/2253 (95%) taking 6-7 tablets per week
- 85% proceeded to randomisation - very similar across all cohorts and close to what was expected (90%)
- Reasons for not proceeding often multi-factorial – main reasons minor toxicity and participant choice
- Only 0.7% (15/2253) experienced toxicity requiring discontinuation during the run-in

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Add-Aspirin Run-In Toxicity

- Most common grade 1-2 toxicities were dyspepsia and bruising
- 13/2253 (0.6%) participants had grade 3 toxicities, between 0.5% and 1.0% in individual tumour groups

		Breast	Colorectal	OG	Prostate
Participants with run-in data available		1113	602	75	463
Dyspepsia	Grade 1-2	138 (12%)	51 (8%)	10 (13%)	47 (10%)
	Grade 3-4	0 (0%)	2 (0%)	0 (0%)	0 (0%)
Bruising	Grade 1-2	133 (12%)	53 (9%)	2 (3%)	23 (5%)
	Grade 3-4	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Lower GI bleed	Grade 1-2	4 (0%)	6 (1%)	1 (1%)	3 (1%)
	Grade 3-4	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Upper GI bleed	Grade 1-2	0 (0%)	1 (0%)	0 (0%)	0 (0%)
	Grade 3-4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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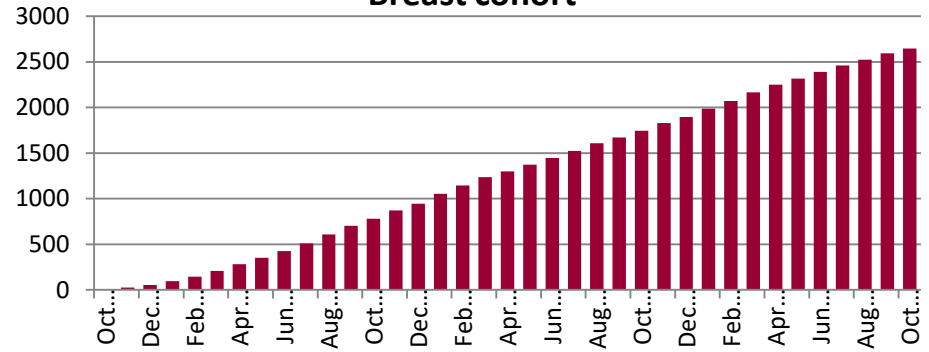
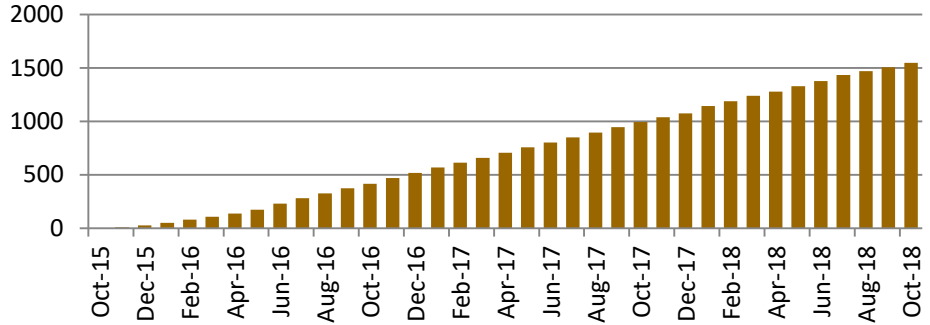
Add-Aspirin Recruitment Update

Cumulative registrations

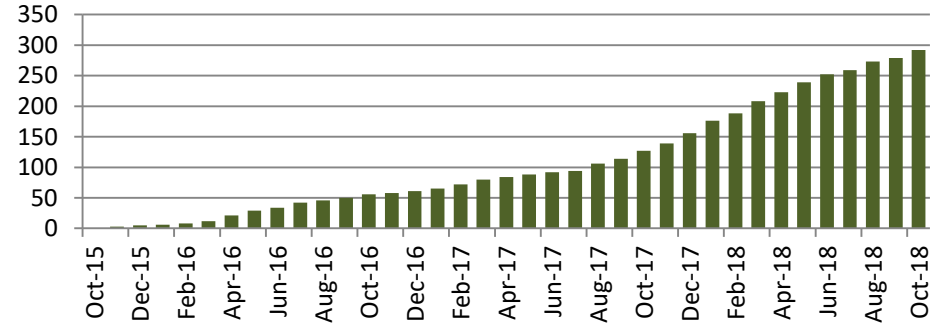
Breast cohort



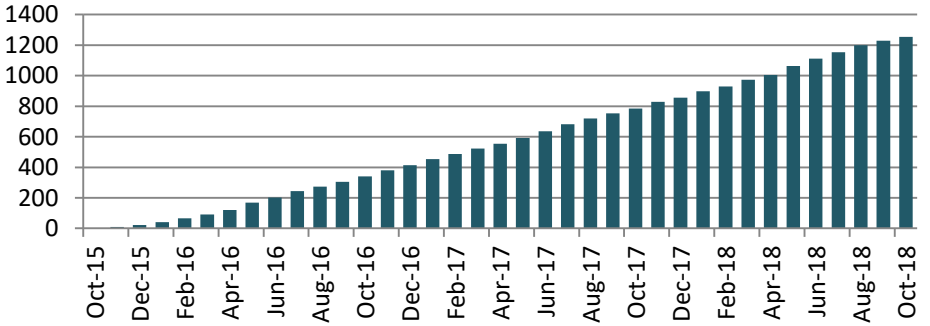
Colorectal cohort



Gastro-oesophageal cohort



Prostate cohort



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Conclusion

- Aspirin acceptable and well-tolerated over an 8-week run-in after radical cancer therapy for common solid tumours, including gastro-oesophageal cancer
- Overall toxicity has been low in the trial and bleeding events are rare
- A run-in approach may be useful in adjuvant studies for reducing the risk of non-adherence and participant attrition
- Recruitment to Add-Aspirin continues, >5700 participants registered in the UK & India and Ireland

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- Bayer Pharmaceuticals AG is providing aspirin and placebos.
- Cipla Inc provide run-in aspirin in India.

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