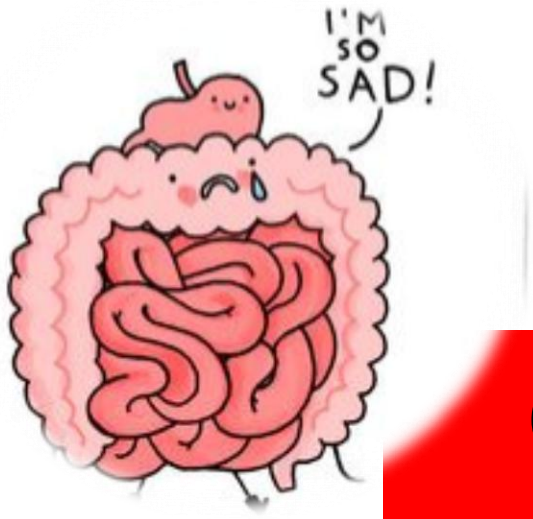


Aspirin for everyone?
Aspirin for no one?

Gut feelings or an evidence-based medicine?

Nadir Arber, MD, MSc, MHA
Head – Health Promotion Center
Head - Integrated Cancer Prevention Center
Tel Aviv Medical Center
and Tel Aviv University

A Quick Reminder

1. **Preventive benefits occur later and under-appreciated**
2. **Failure to prevent is an act of omission- less regret**
3. **Should start at age 40-50 year**
4. **Benefits seen after >5 years**
5. **Benefit unrelated to dose!!!! 100mg=600mg, 325?**
6. **Low dose aspirin is sufficient**
7. **Effect is maximized after 10-15 years**
8. **Should not initiated in the elderly (>75 year) (ASPREE)**
9. **Protects from Alzheimer disease!!!!**
10. **Reduces overall mortality**
11. **Low profile of side effects**
12. **Genomic molecular signature predict efficacy and toxicity**
13. **Cancer incidence decrease as do major bleeding events with extended aspirin use**

43 CAPP2 recruiting centres:
1009 Lynch syndrome recruits

UK

Aberdeen, Edinburgh, Glasgow, Newcastle, Leeds
Sheffield, Manchester, Liverpool, Birmingham, Cardiff,
Belfast, Oxford, Bristol, St Marks, St Georges, Guys-London
Southampton, Exeter, Guildford, Worthing

Rest of Europe

Finland, Sweden, Denmark, Germany,
Belgium, Poland, Netherlands, France,
Hungary, Switzerland, Portugal, Spain, Italy

Australia

Melbourne
Brisbane
Newcastle
Perth

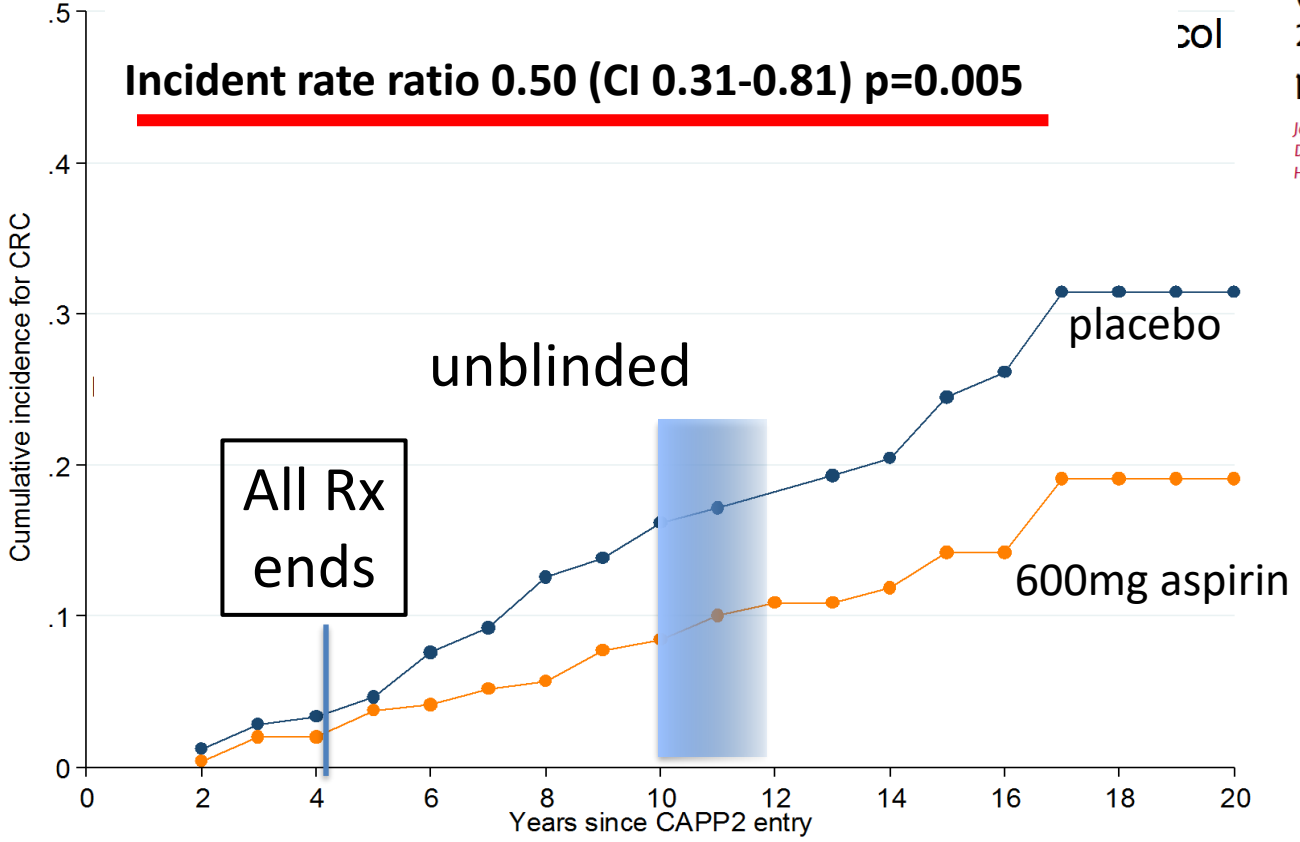
600mg aspirin /day versus placebo
Average for 29 months
Mean age 45 years
1999 - 2007

CaPP2: Planned 10 yr review PLUS national registry data aspirin cancer prevention persists for over a decade

Intention to treat HR 0.65 (95% CI 0.43-0.97) p= 0.04

Per Protocol HR 0.56 (95% cI 0.34-0.91) p=0.02

Incident rate ratio 0.50 (CI 0.31-0.81) p=0.005



HR = Hazard Ratio (counts first cancer). IRR = Incident Rate Ratio (counts all cancers)

Articles

Lancet 2020; 395: 1855–63

Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial

John Burn, Harsh Sheth*, Faye Elliott*, Lynn Reed, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Möslein, Fiona E McRonald, Lucio Bertario, D Gareth Evans, Anne-Marie Gerdes, Judy W C Ho, Annika Lindblom, Patrick J Morrison, Jem Rashbass, Raj Ramesar, Toni Seppälä, Huw J W Thomas, Kirsi Pylvänäinen, Gillian M Borthwick, John C Mathers, D Timothy Bishop, on behalf of the CAPP2 Investigators

For every 25 LS patients treated with 600mg aspirin, one colorectal cancer is prevented over ~15 years (effect starts from 5 years).

No signif. Difference in side effects


NICE National Institute for Health and Care Excellence

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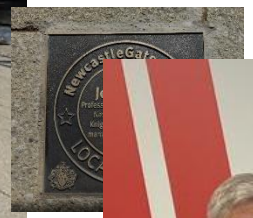
Offer daily aspirin to those with inherited genetic condition to reduce the risk of colorectal cancer

Aspirin taken daily for 2 years or more could reduce the risk of colorectal cancer

Israel Joins CaPP3



entre for Life
astle University

CaPP3 International Collaboration

CaPP3 Statistical Analysis Plan 2014

"…..**a non-inferiority study** …..baseline 600mg aspirin/day compared separately to two lower trial doses; **non-inferiority will be declared if … effect on cancer incidence is less than 1.5 times worse than the standard 600 mg dose**.

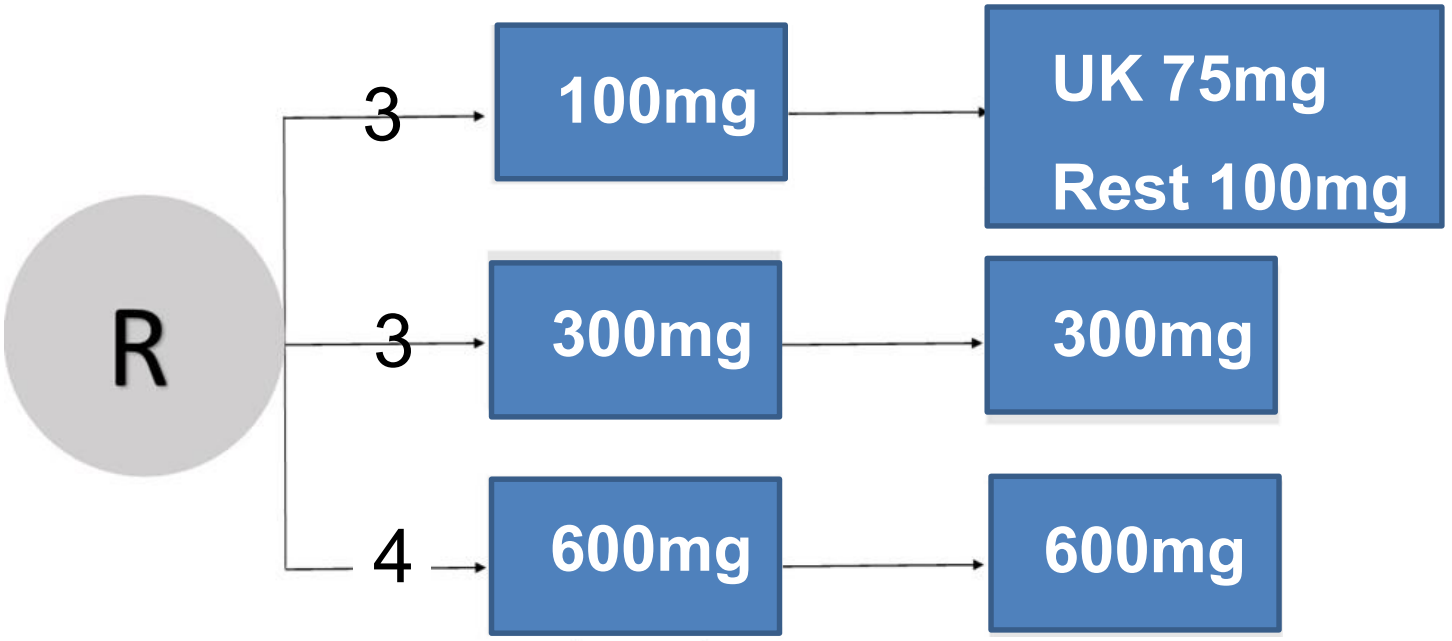
Jones, B., P. Jarvis, J. A. Lewis, and A. F. Ebbutt. 1996.
'Trials to assess equivalence: the importance of rigorous methods', *BMJ*, 313: 36-9.

"To compare the overall cumulative incidence of **LS cancers** using **Cox proportional hazards for time to first LS cancer** ……and **negative binomial regression (NBR) to allow for multiple primaries**

Incidence Rate Ratios (IRR) for the effect of aspirin will be estimated from log-linear models **for the number of primary cancers**…"

1866 Lynch syndrome gene carriers

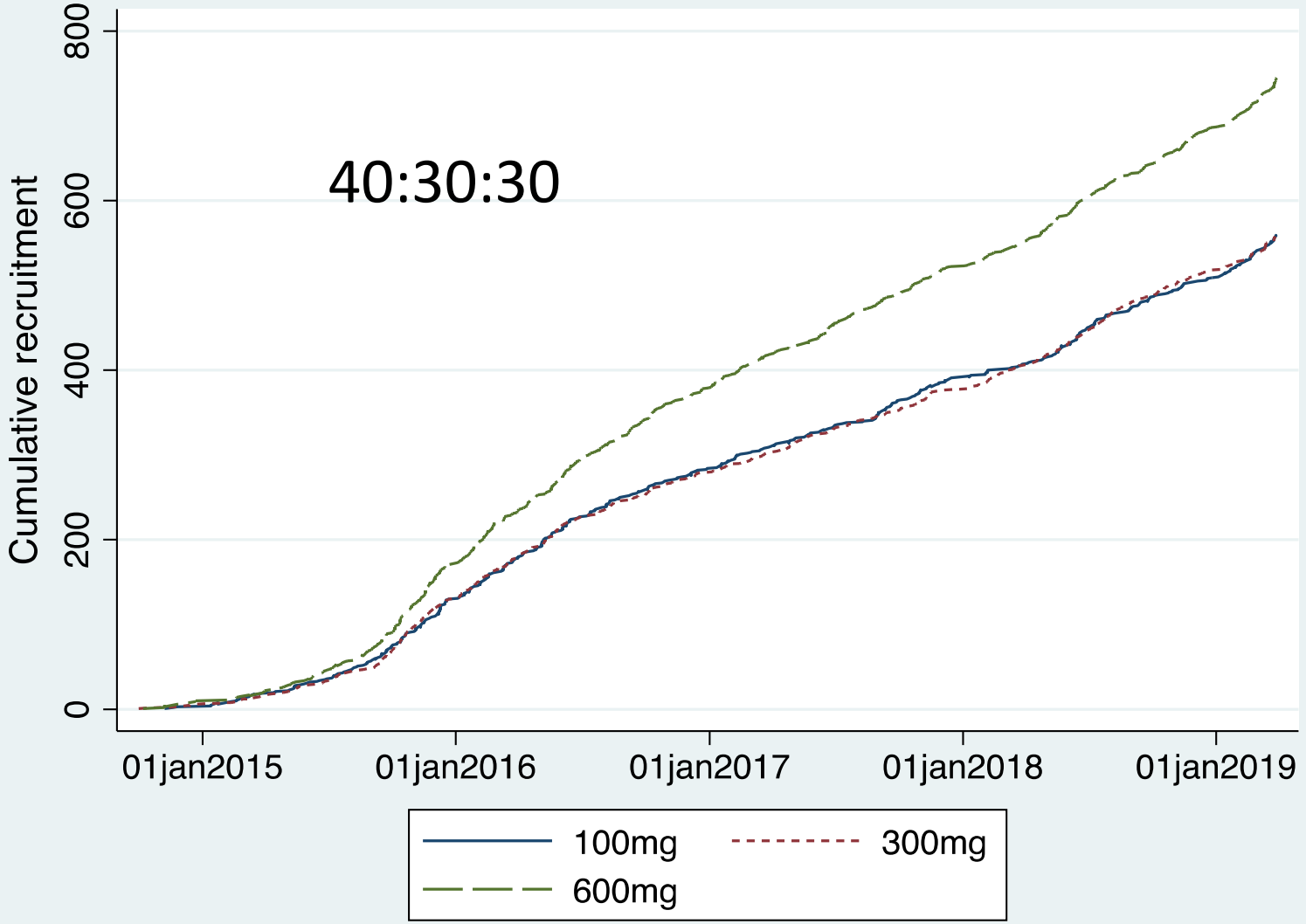
Dose non-inferiority randomised trial



Open Phase: maintain equivalent dose

FPFV 2014
End blinded stage 2021
LPLV 2024

recruitment



1866 Eligible recruits

	%
MSH2	39.4%
MLH1.	32.4%
MSH6	19.5%
PMS2	7.6%
EPCAM	1.0%
Epimut	0.1%

Mean age 46.3 years

Prevention trials take a long time
What aspirin dose?

- Recruitment started 1st October 2014
- Recruitment finished 31st March 2019
- International total **312**
- Israel **51**
- **Total 1879** recruits
- Initial analysis of cancer incidence @ 5 years 2024/25
- Long term cancer follow up – 10 years

Recruitment closed 31.03.19

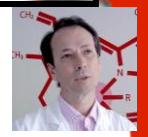
Participant follow up ongoing
Remaining open during COVID
Initial analysis in 2024_25 (NCRAS)

Total recruitment 1879
31 March 2019

CaPP3 Finland
77 recruits

CaPP3 Israel
51 recruits

CaPP3 Spain
43 recruits



UK
26 Sites
1567 recruits

CaPP3 Australia
141 recruits

Parallel data sharing studies

CaPP3 Australia: CI Professor Finlay Macrae
CaPP3 Finland: CI Professor Jukka-Pekka Mecklin
CaPP3 Israel: CI Professor Nadir Arber
CaPP3 Spain: CI Dr Ángel Alonso Sánchez

CANCER RESEARCH UK

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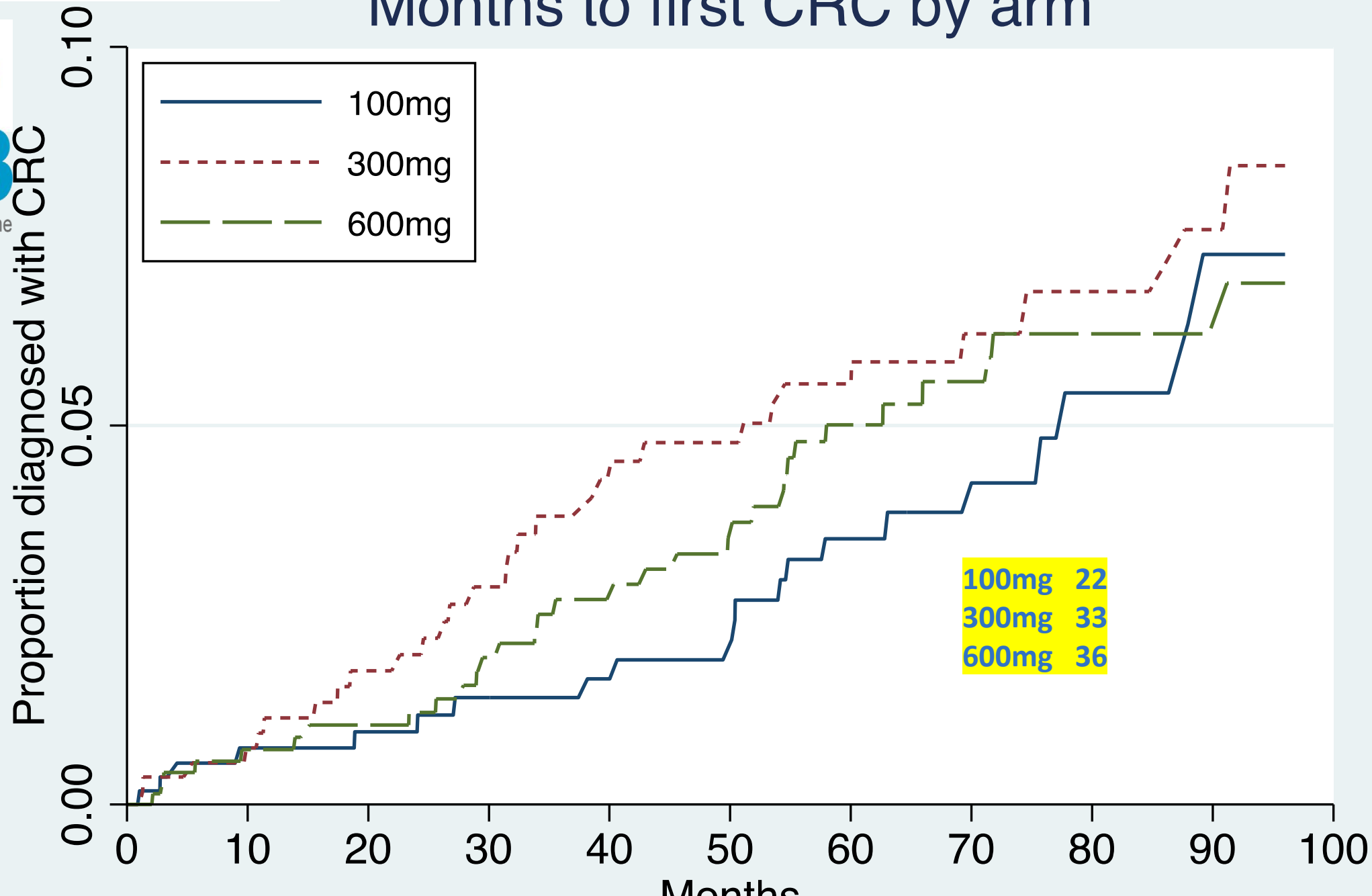
Cancer Prevention Programme

Months to first CRC by arm



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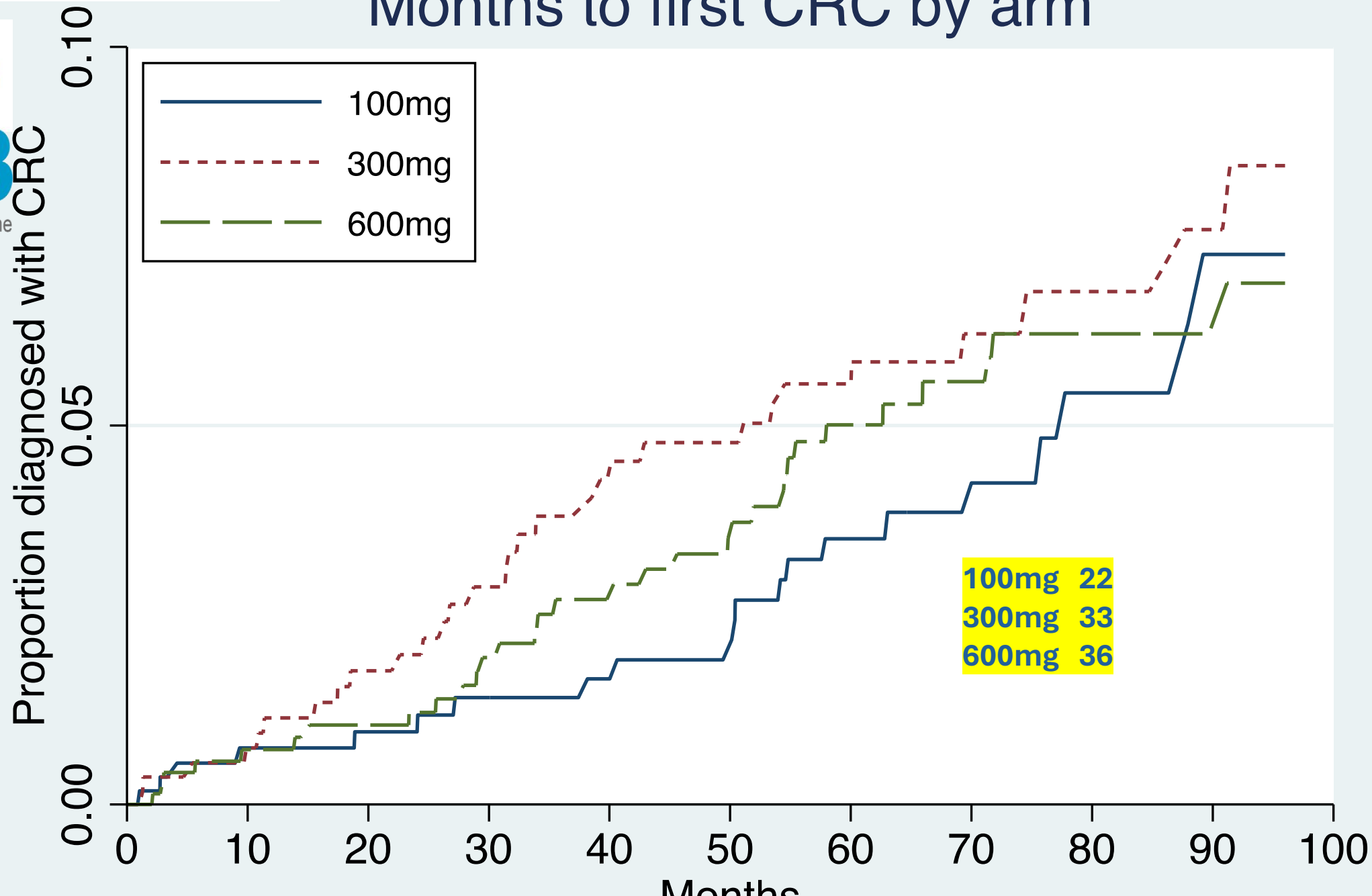
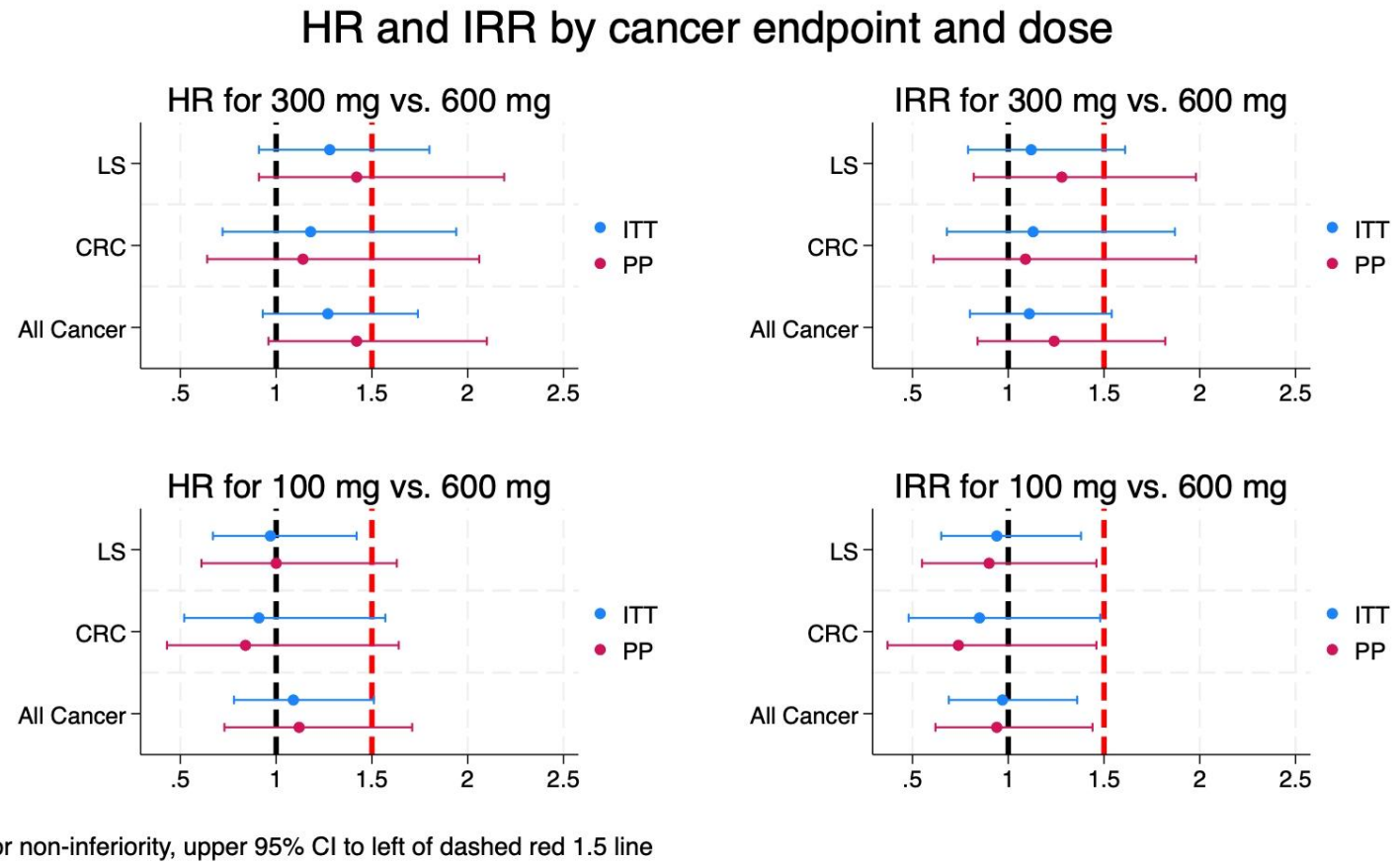
Cancer Prevention Programme

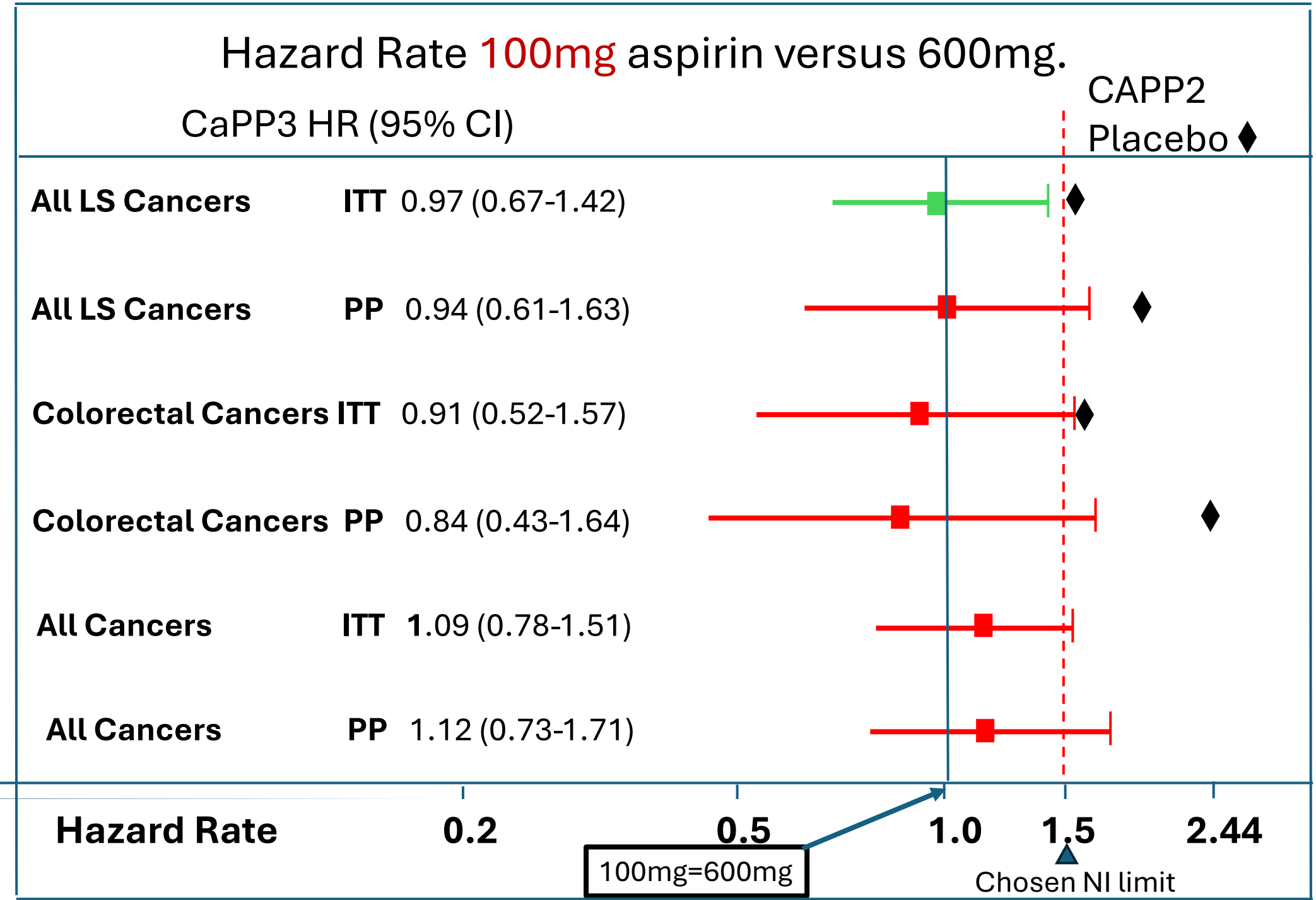


Cancer Prevention with aspirin in hereditary cancer due to MisMatch Repair deficiency (Lynch syndrome): first results from the CaPP3 Dose Non-Inferiority randomised clinical trial.

Figure 4



Hazard Rate 100mg aspirin versus 600mg.



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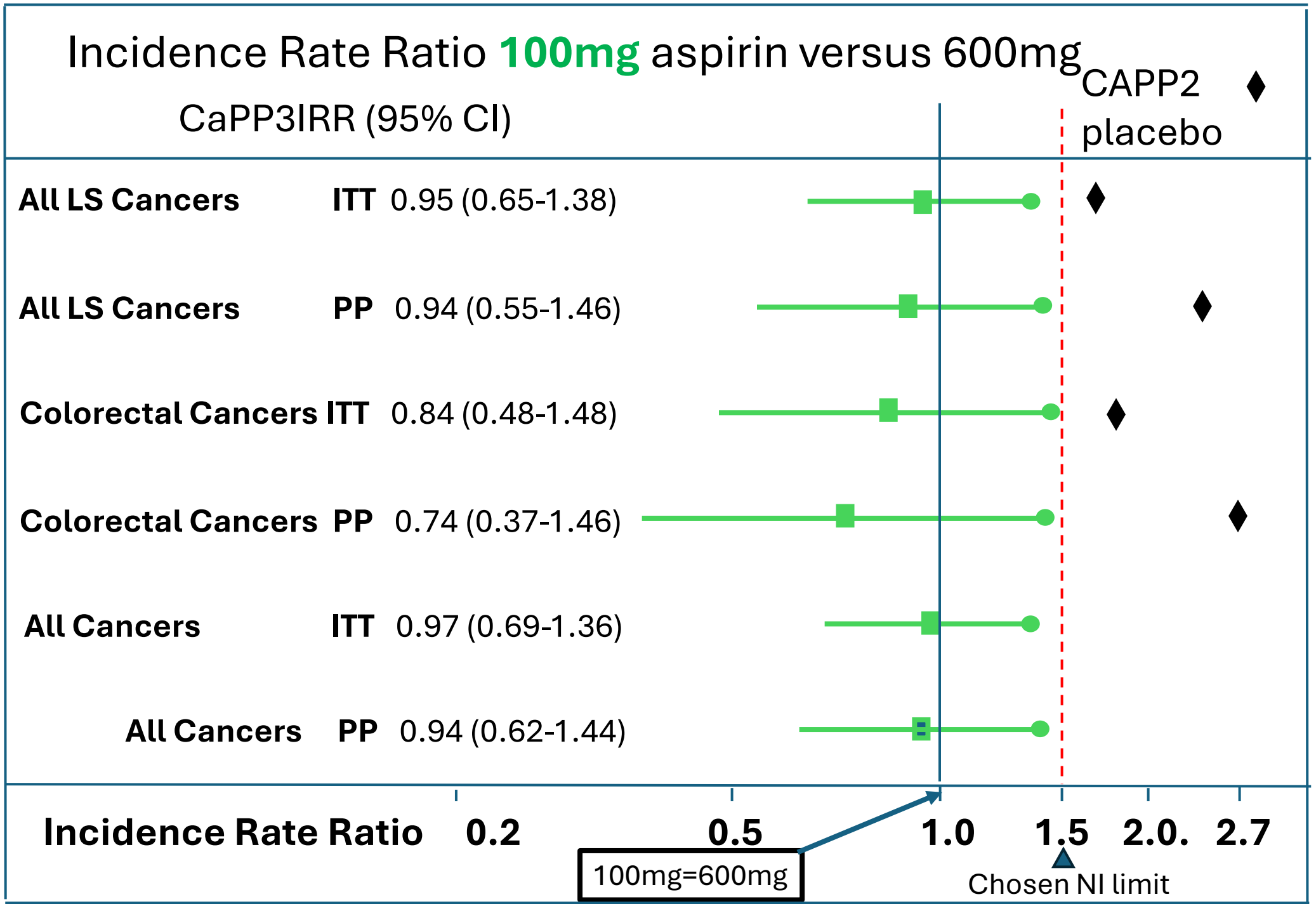
Incidence Rate Ratio **100mg** aspirin versus 600mg



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Cancer Prevention Programme

Unpublished: do not reproduce

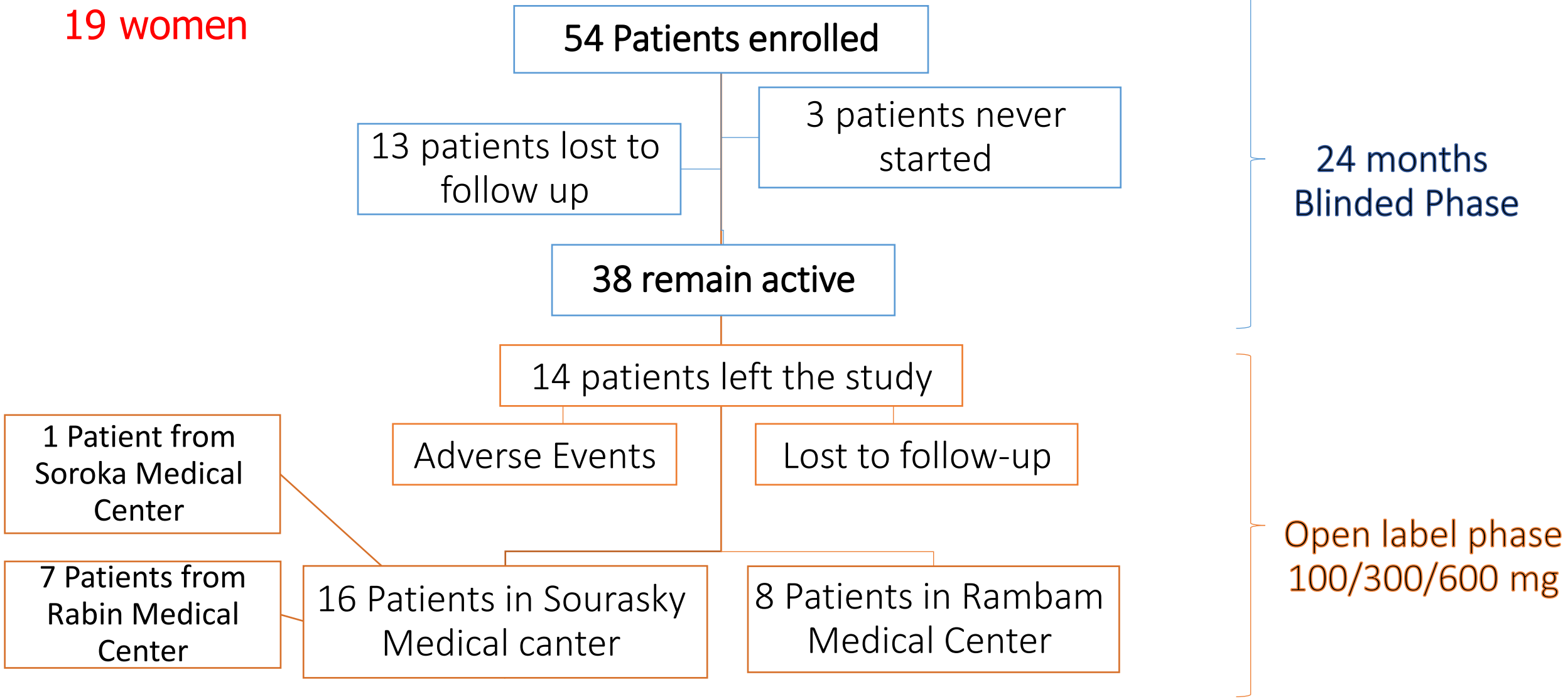
Serious Adverse Events: 96 months

	100mg	300mg	600mg
Total	26	30	47
Bleeds.	0 *(0%)*	3 *(0.5%)*	11 *(1.5%)*

Fisher's exact test, p=0.004

CAPP3 participants

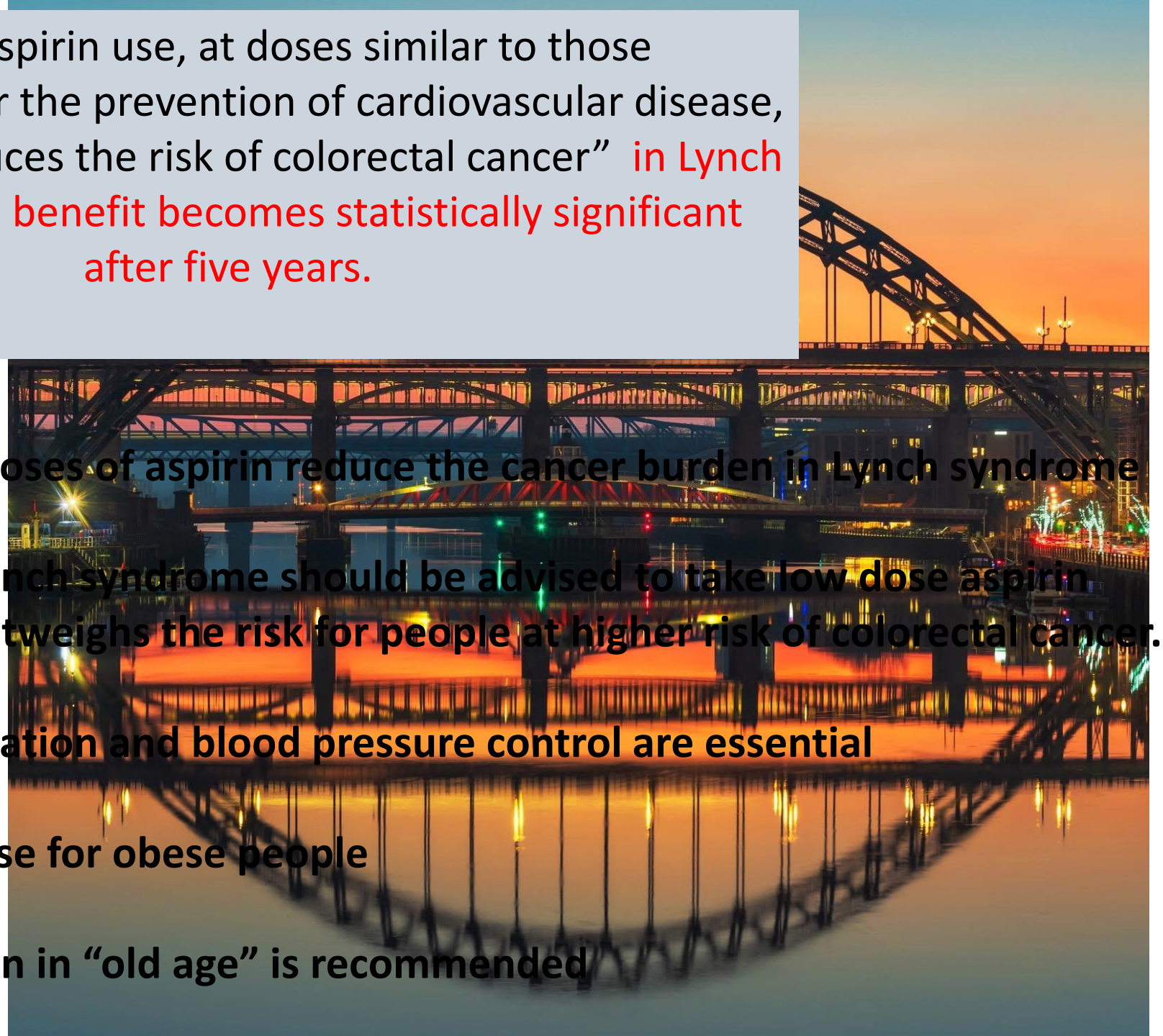
Mean age - 46yr
32 males
19 women



Outcomes

- One death
- One CRC (100mg)
- One prostate cancer (300mg)
- No SAEs
- 11 with AEs
  - GI (1, 2, 2)
  - Bleeding (2, 2, 1)

“Regular aspirin use, at doses similar to those recommended for the prevention of cardiovascular disease, substantially reduces the risk of colorectal cancer” in Lynch syndrome. The benefit becomes statistically significant after five years.



- **Anti-platelet doses of aspirin reduce the cancer burden in Lynch syndrome**
- **People with Lynch syndrome should be advised to take low dose aspirin**
- **The benefit outweighs the risk for people at higher risk of colorectal cancer.**
- **H Pylori eradication and blood pressure control are essential**
- **Double the dose for obese people**
- **Discontinuation in “old age” is recommended**

CaPP3

Cancer Prevention Programme

UK PIs

ABERDEEN	Zosia Miedzybrodzka
BELFAST	Patrick Morrison
BIRMINGHAM	Kai Ren Ong
BRISTOL	Alan Donaldson
CAMBRIDGE	Ruth Armstrong
CARDIFF/SWANSEA	Alex Murray
DUNDEE	Jonathan Berg
EDINBURGH	Jennie Murray
EXETER	Ruth Cleaver
GLASGOW	Rosemarie Davidson
GOSH	Ajith Kumar
LEEDS	Alison Kraus
LEICESTER	Julian Barwell
LIVERPOOL	Rachel Hart
LONDON GUYS	Adam Shaw
MANCHESTER	Emma Woodward
NOTTINGHAM	Rachel Harrison
OXFORD	Dorothy Halliday
ROYAL MARSDEN	Zoe Kemp
RHYL	Carrie Pottinger
ST GEORGES	Katie Snape
SHEFFIELD	Jackie Cook
ST MARKS	Huw Thomas
SOUTHAMPTON	Lucy Side
NEWCASTLE	John Burn

& all the research teams at each centre

Official Sponsor

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The Newcastle upon Tyne Hospitals
NHS Foundation Trust

CaPP3 Australia

The Royal Melbourne Hospital

Finlay Macrae
Zafirah Khan
Mary Franich
Ingrid Winship
Alex Boussioutas
Kathy Wu
James Toh
Helen Mar Fan
Louise Lynagh
Isabelle Danos
Cassandra Mcdonald

CaPP3 Finland

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Kirsi Pylvänäinen
Toni Seppälä
Laura Renkonen-Sinisalo

CaPP3 Spain

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AsCaP
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