

CHIP for polyposis day

Dr Warren Hyer
Consultant Paediatric Gastroenterologist
Northwick Park and St Mark's Hospital

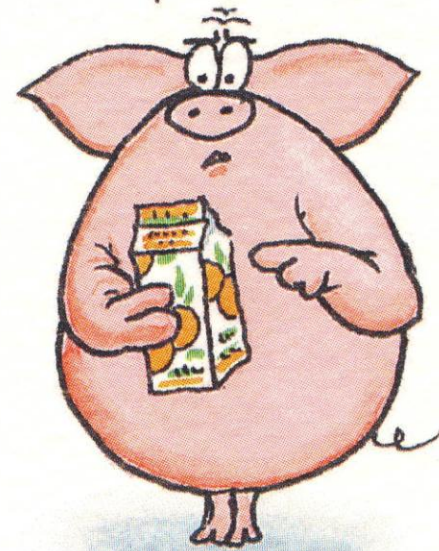
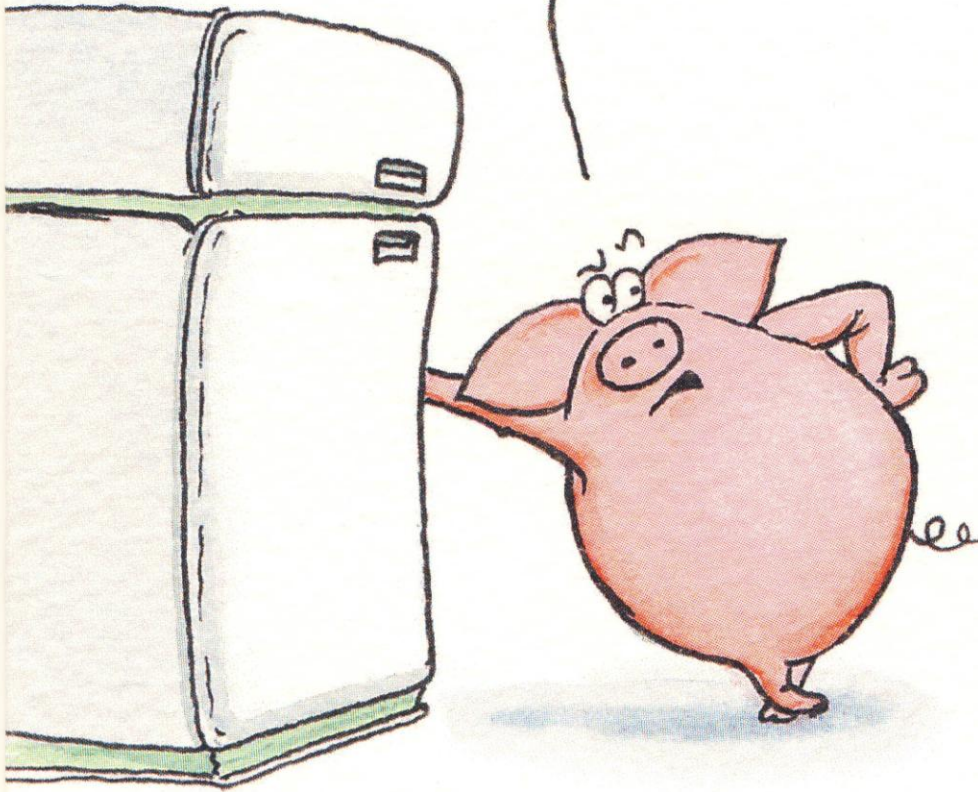


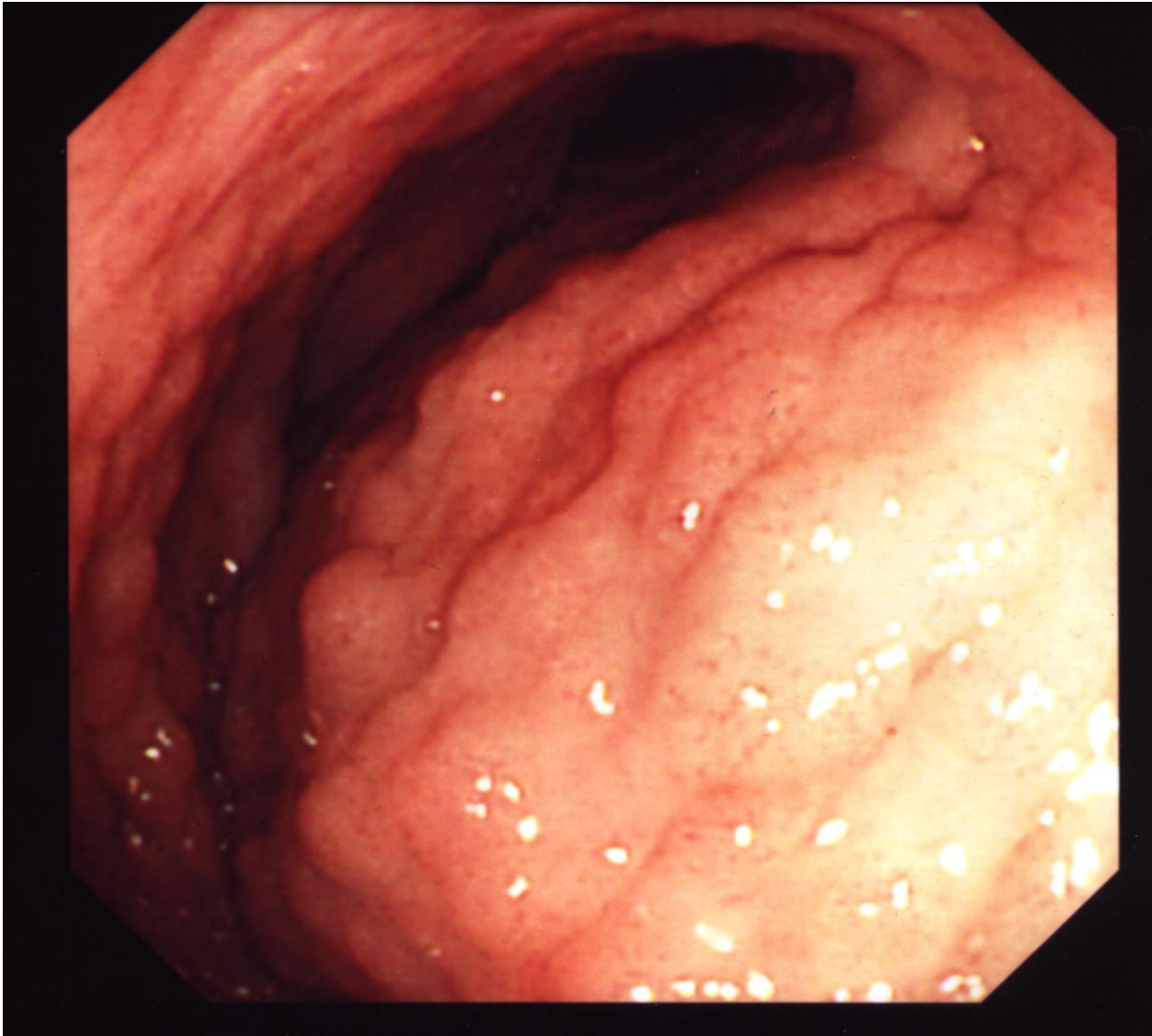
Conflict of interest - independency

- Neither myself, nor Sue Clark, (principal investigator) receive payment nor benefits from the CHIP study.

Warren, you've been staring at that carton of orange juice for half an hour. What's the problem?

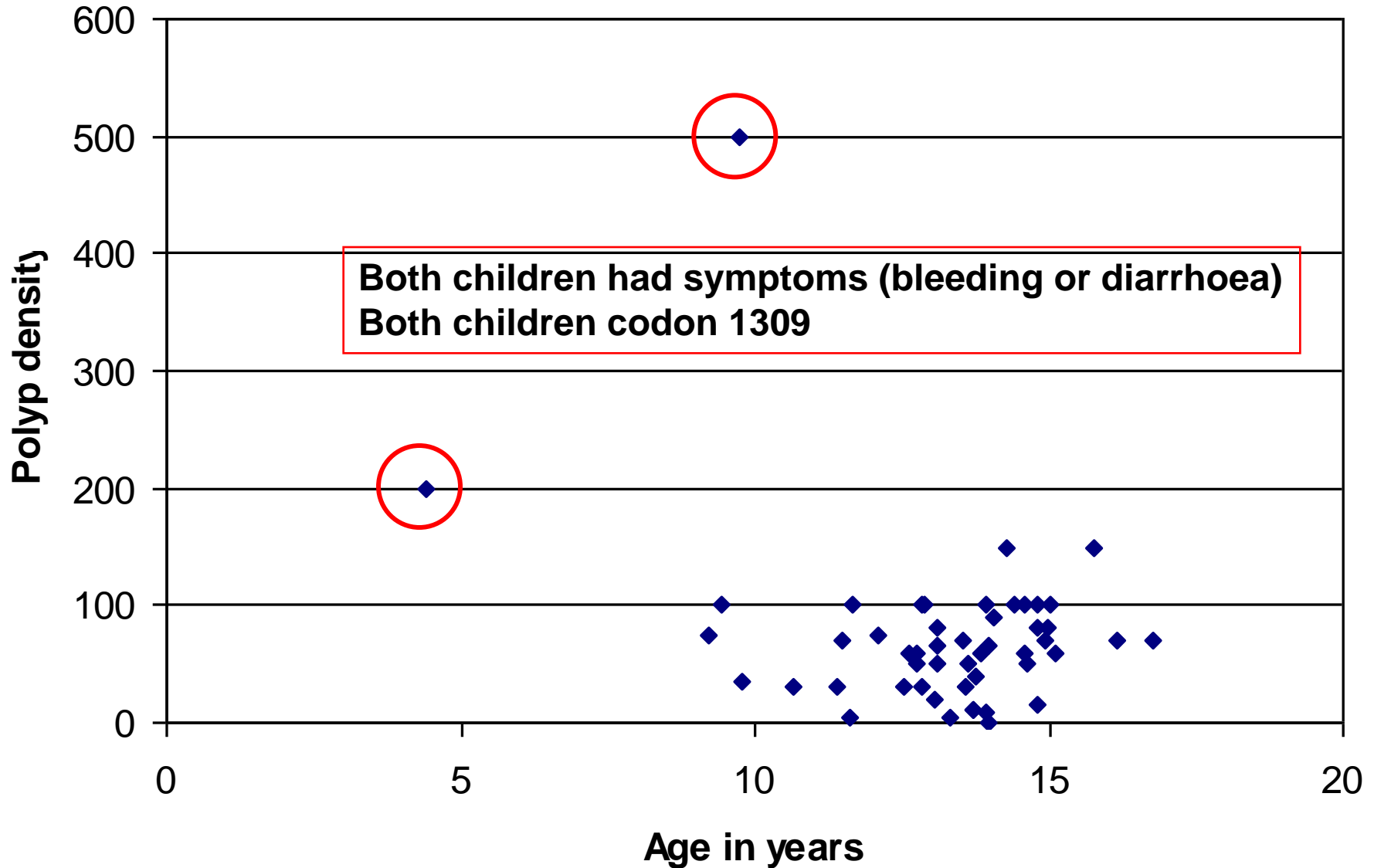
Sssh! It says concentrate.







Which children had high polyp density?





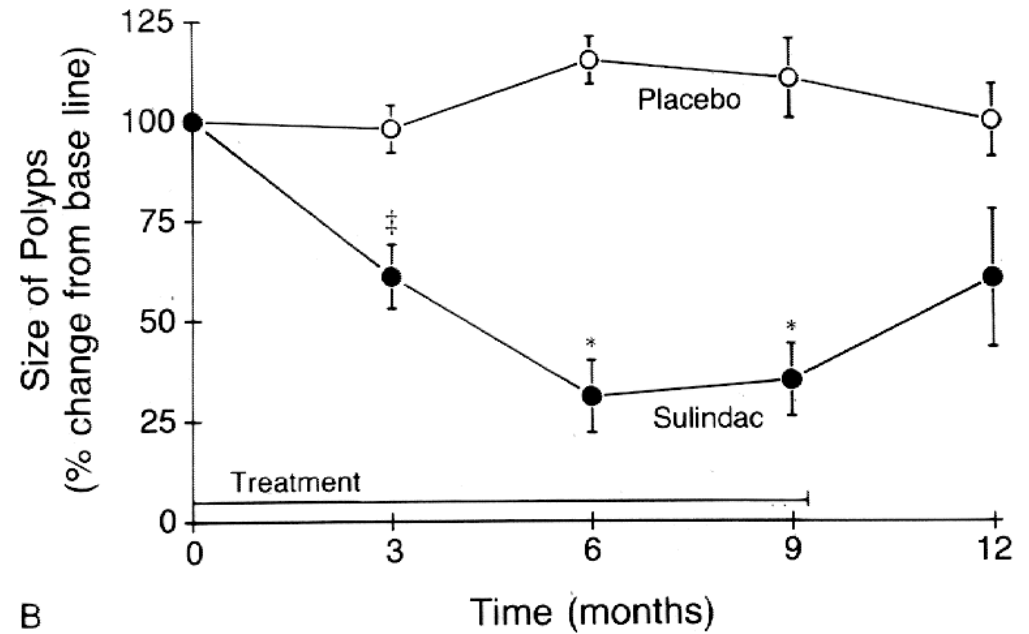
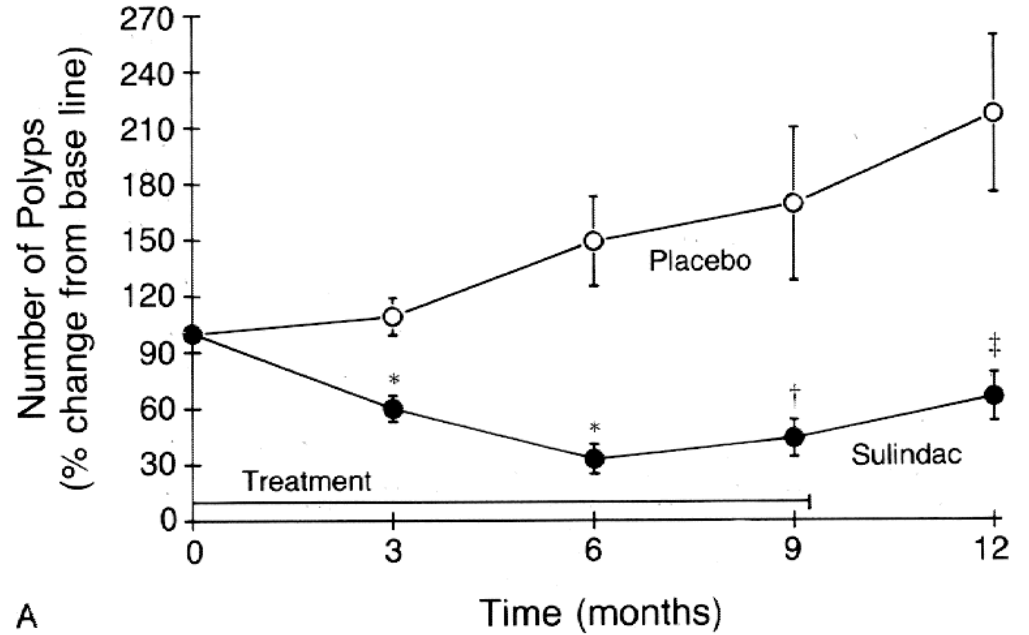
Now the chance for
adenoma prevention?

What medicines might reduce or prevent polyps

- Aspirin
- Aspirin type drugs – NSAID
- Sulindac
- COX 2 inhibitor medicines – e.g. celecoxib

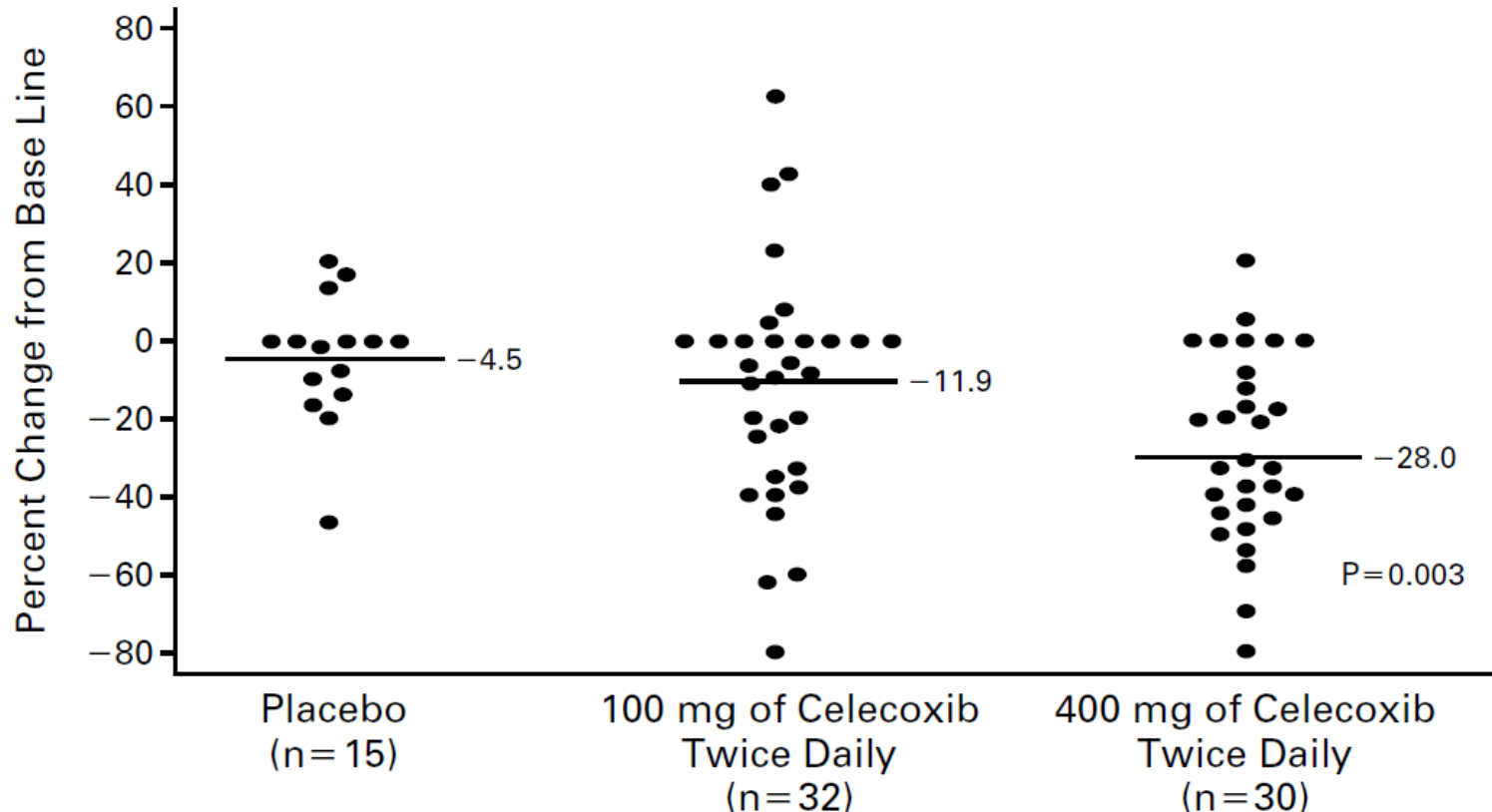
**NEJM 328:1313-1316 1993
Treatment of Colonic and
Rectal Adenomas with
Sulindac in
Familial Adenomatous
Polyposis**

Francis M. Giardiello



THE EFFECT OF CELECOXIB, A CYCLOOXYGENASE-2 INHIBITOR, IN FAMILIAL ADENOMATOUS POLYPOSIS

GIDEON STEINBACH, M.D., PH.D., PATRICK M. LYNCH, M.D., J.D., ROBIN K.S. PHILLIPS, M.B., B.S., MARINA H. WALLACE, M.B., B.S., ERNEST HAWK, M.D., M.P.H., GARY B. GORDON, M.D., PH.D., NAOKI WAKABAYASHI, M.D., PH.D., BRIAN SAUNDERS, M.D., YU SHEN, PH.D., TAKASHI FUJIMURA, M.D., LI-KUO SU, PH.D., AND BERNARD LEVIN, M.D.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Celecoxib for the Prevention of Colorectal Adenomatous Polyps

Nadir Arber, M.D., Craig J. Eagle, M.D., Julius Spicak, M.D., István Rácz, M.D.,

The NEW ENGLAND
JOURNAL of MEDICINE

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Celecoxib for the Prevention of Sporadic Colorectal Adenomas

Monica M. Bertagnolli, M.D., Craig J. Eagle, M.D., Ann G. Zauber, Ph.D., Mark Redston, M.D.,



Does it increase the risk of heart disease?

- Depression of I₂ prostaglandin formation
- Elevate blood pressure
- Accelerate atherogenesis
- Thus exaggerated thrombotic response

“The higher a patient’s intrinsic risk of cardiovascular disease the more likely it would be that such a hazard would manifest itself rapidly in the form of a clinical event”

insignificant
in an adolescent

Risk from inevitable polyps made in the colon by FAP patients

Likely Insignificant Risk from COX 2 on heart

Potential Protection By COX 2

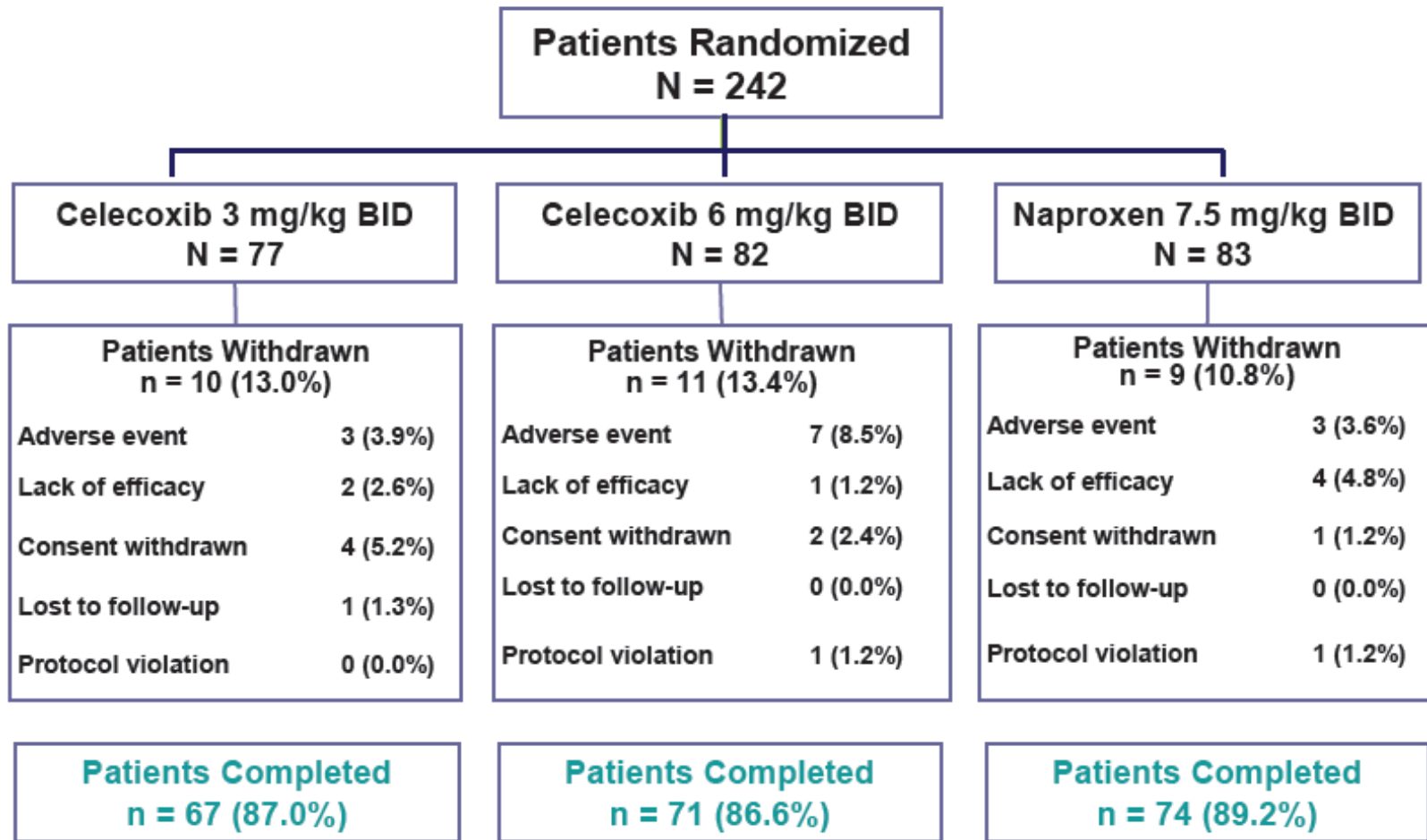
CVS risks of COX -2 inhibitors outweigh the potential chemopreventive benefits with sporadic colorectal adenomas – this is not so for FAP

- But the FAP cohort are significantly younger than the PreSaP cohort.
- Do they confer the same CVS risk?
- What paediatric data exists with COX2 inhibitors?



JRA studies in children celecoxib

Double-Blind Phase



Side effects

- Same as with brufen
- Mild abdominal pain
- ? Bit of fever
- No significant events

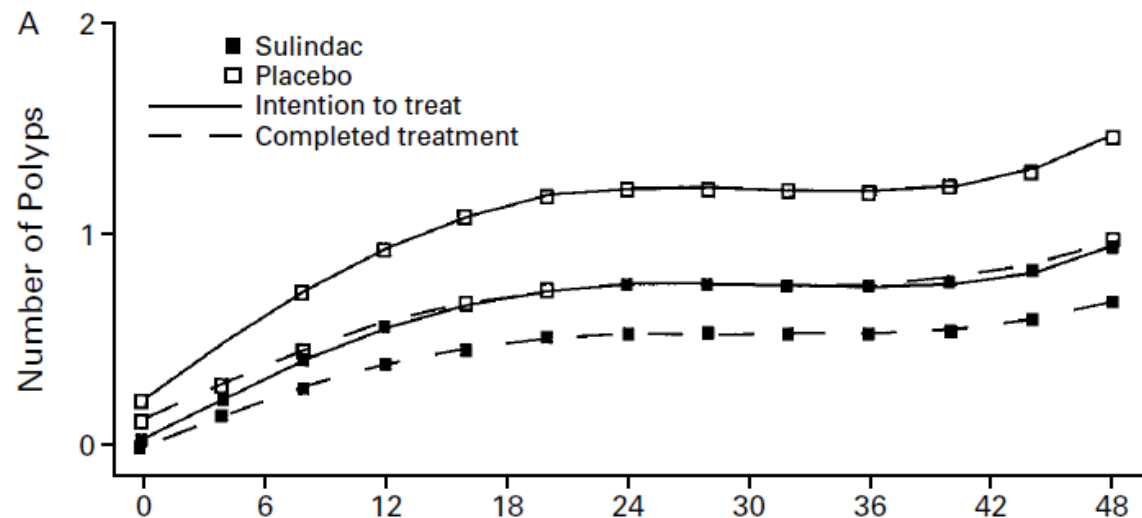
Adenoma prevention with sulindac

The New England Journal of Medicine

PRIMARY CHEMOPREVENTION OF FAMILIAL ADENOMATOUS POLYPOSIS WITH SULINDAC

FRANCIS M. GIARDIELLO, M.D., VINCENT W. YANG, M.D., PH.D., LINDA M. HYLIND, B.S., R.N., ANNE J. KRUSH, M.S., GLORIA M. PETERSEN, PH.D., JILL D. TRIMBATH, M.S., STEVEN PIANTADOSI, M.D., PH.D., ELIZABETH GARRETT, PH.D., DEBORAH E. GEIMAN, M.S., WALTER HUBBARD, PH.D., G. JOHAN A. OFFERHAUS, M.D., M.P.H., PH.D., AND STANLEY R. HAMILTON, M.D.

Sulindac did not slow the development of adenomas



The Safety and Efficacy of Celecoxib in Children With Familial Adenomatous Polyposis

Patrick M. Lynch, MD, JD¹, Gregory D. Ayers, MS², Ernie Hawk, MD, MPH³, Ellen Richmond, RN, MSN³, Craig Eagle, MD⁴, Mabel Woloj, PhD⁴, James Church, MD⁵, Hennie Hasson, RN⁶, Sherri Patterson, RN⁷, Elizabeth Half, MD⁸ and Carol A. Burke, MD⁸

Table 1. Celecoxib dose assignments by body weight and cohort

	Cohort 1, <i>n</i> =6 (2:1 drug: placebo)	Cohort 2, <i>n</i> =6 (2:1 drug: placebo)	Cohort 3, <i>n</i> =6 (2:1 drug: placebo)
Body weight	Celecoxib dose 4 mg/kg	Celecoxib dose 8 mg/kg	Celecoxib dose 16 mg/kg
25.0–37.5 kg	50 mg BID	100 mg BID	200 mg BID
37.6–50.0 kg	100 mg BID	150 mg BID	300 mg BID
>50.0 kg	100 mg BID	200 mg BID	400 mg BID

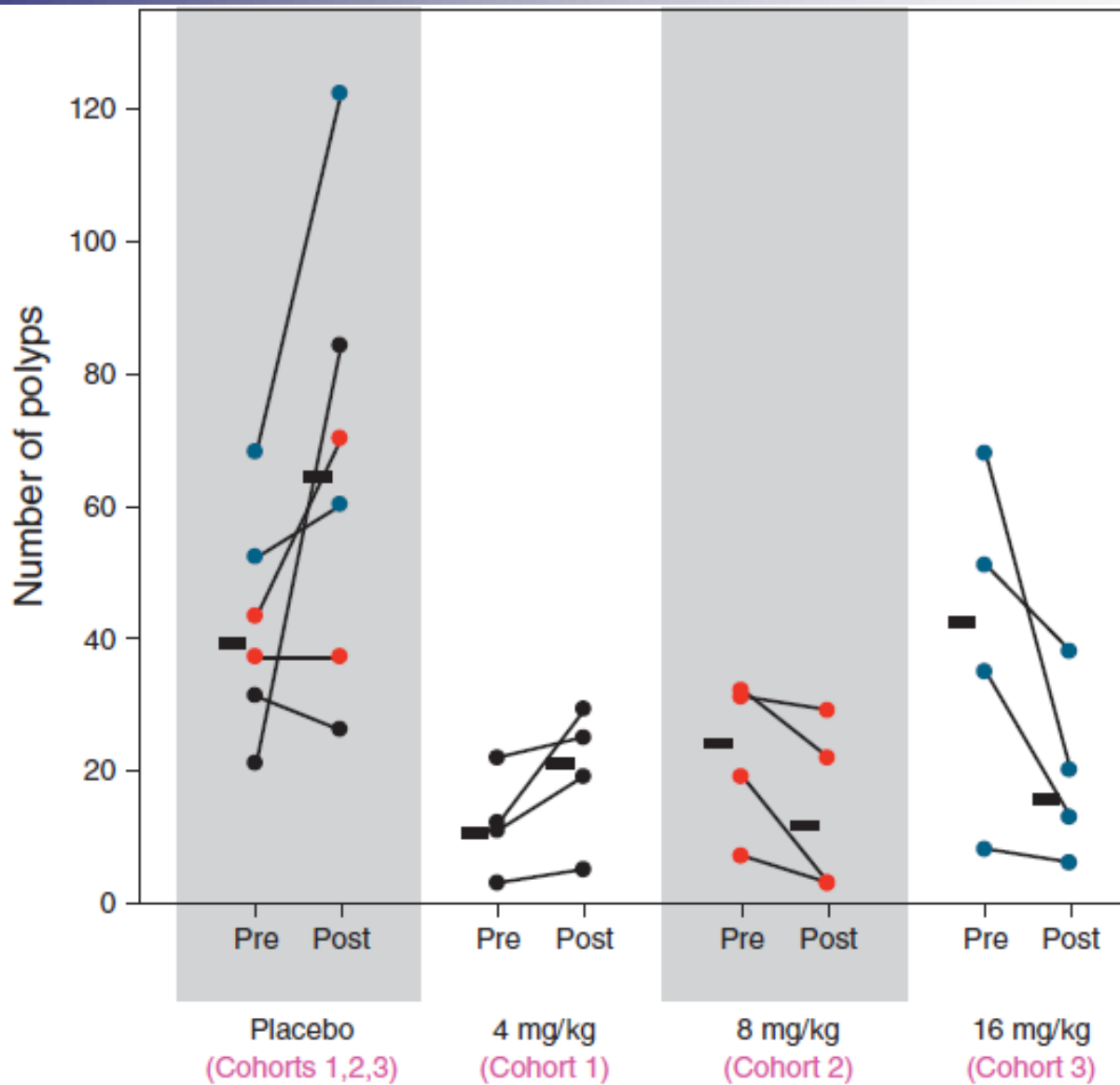


Figure 2. Celecoxib dose–response relationship among pediatric patients with familial adenomatous polyposis. The number of polyps at baseline

Phase I Pediatric Celecoxib Trial Adverse Events

Rx Group	Grade I	Grade II
Placebo	24	0
4 mg/kg/d	22	2 (N&V, diarrhea, < 3 d)
8 mg/kg/d	5	2 (nausea, HA, < 1 d)
16 mg/kg/d	21	0

How would the study work



- Age 10-17
- Not too many polyps
- Remove those polyps – start with a clear bowel
- Consent
- Randomise
- Look at the colon every year

Consent

- Study is voluntary and does not impact on the standard of your care that you receive.

THE POLYPOSIS REGISTRY



ST MARK'S
HOSPITAL



Children's International
Polyposis Trial

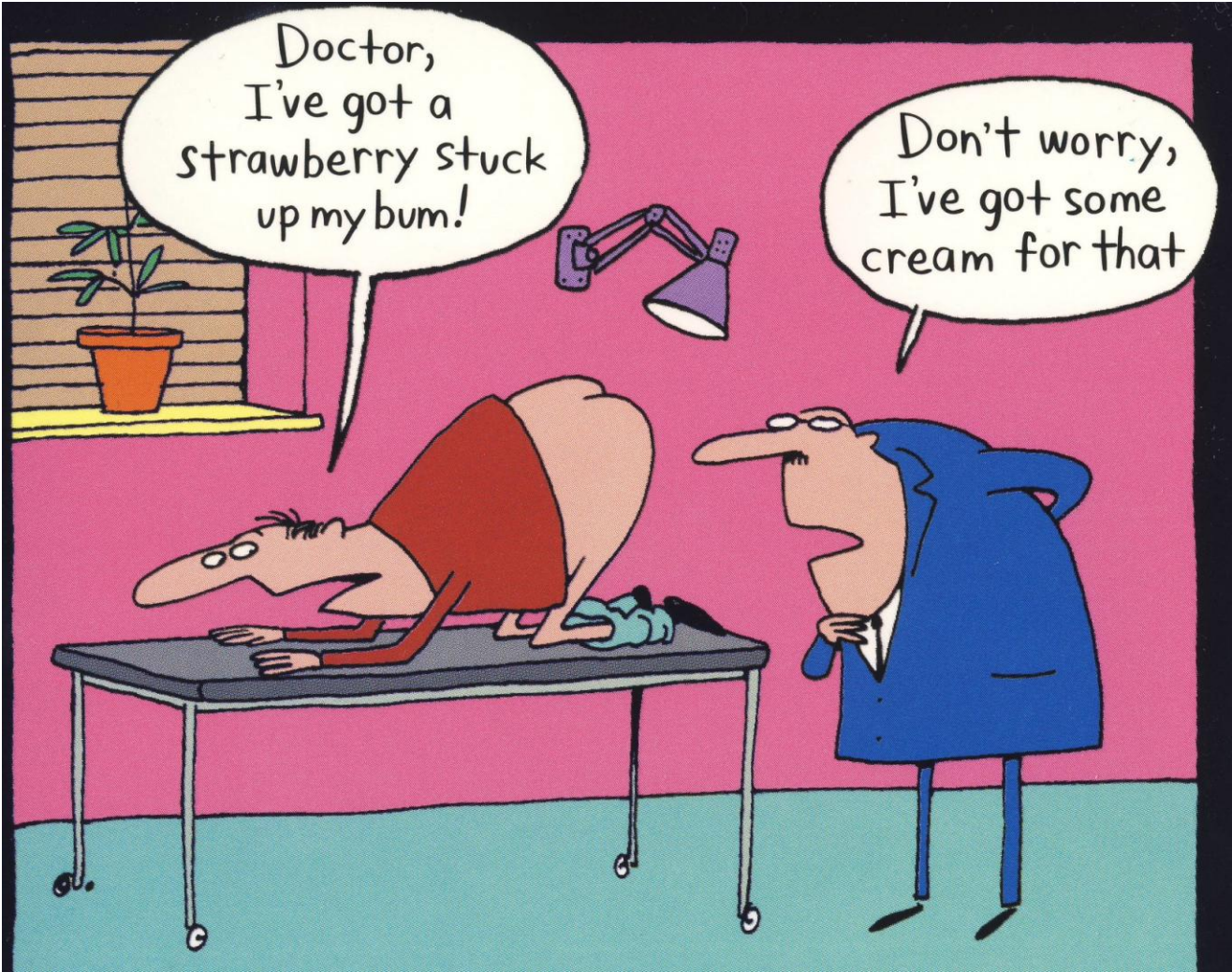
- Sue Clark & Professor Phillips
- Warren Hyer, Jo Rawlings, Chris Fraser
- Polyposis Registry, St Mark's Hospital
- Medicines in children research network

Why bother doing the study?

- Celecoxib could be used as an adjunct to regular surveillance
- Information about the safety and pharmacokinetics of COX 2 inhibitors in children – supporting its long term use if applicable



How many patients
are in the study?



Doctor,
I've got a
strawberry stuck
up my bum!

Don't worry,
I've got some
cream for that