Effect of Celecoxib on Adenoma Count using a Zero-inflated Poisson (ZIP) Model with Random Effects

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Background

- Colorectal cancer (CRC) is the second leading cause of cancer deaths in the US
- CRC is one of the most preventable cancers
  - Most CRC develop from precursor adenomas which can be identified and removed during screening colonoscopy
- NSAIDs, including aspirin, may reduce the incidence of adenomas, CRC, and deaths from CRC
  - NSAIDs are non-specific inhibitors of cyclooxygenases (COX)
  - Overexpression of COX2 can lead to oncogenic responses
- Celecoxib (Celebrex) is a COX2-specific inhibitor used for treatment of arthritis
- Several clinical trials were launched in 1999-2000 to study effect of Celecoxib on prevention of adenomas

Design of Adenoma Prevention with Celecoxib (APC)

Men and women age 30 or older
with large or multiple colorectal adenomas

↓

2035 patients randomized to:

celecoxib 200mg bid N=685	celecoxib 400mg bid N=671	placebo bid N=679

***stratified by low-dose aspirin use and clinical center**

↓

Study medication continued for 3 years after randomization

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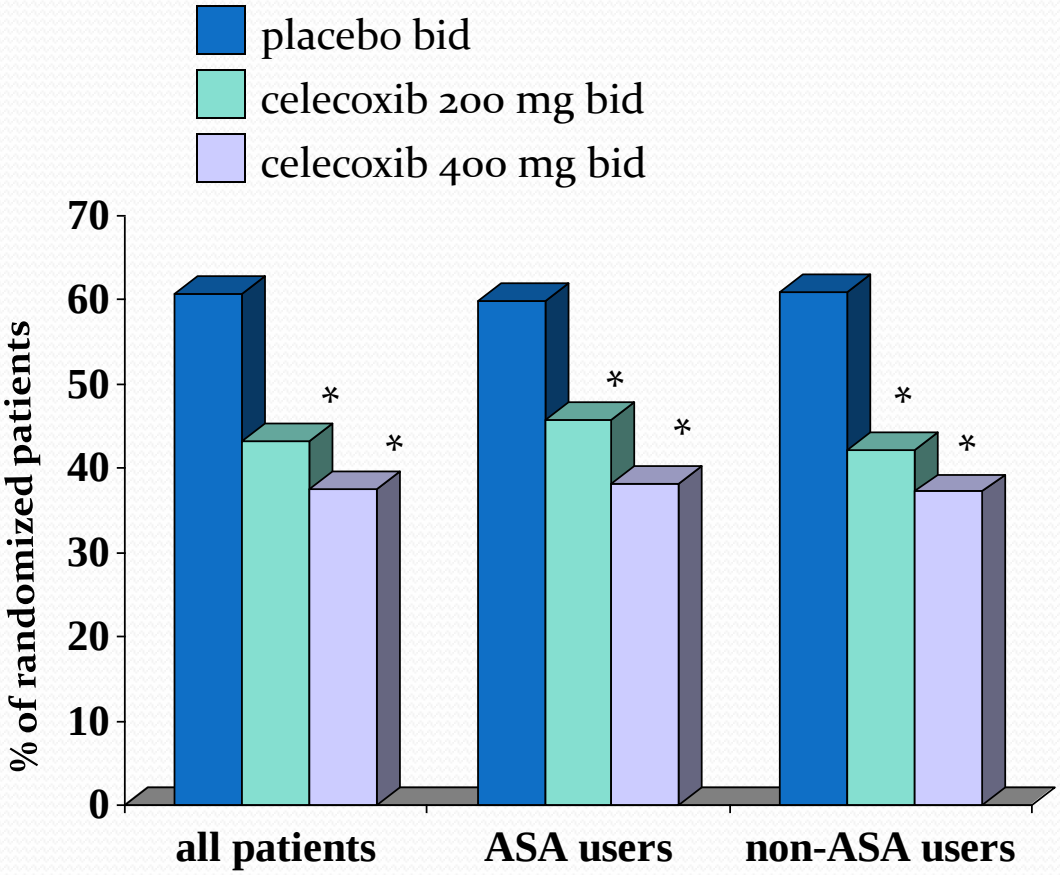
Colonoscopy at 1 and 3 years after randomization

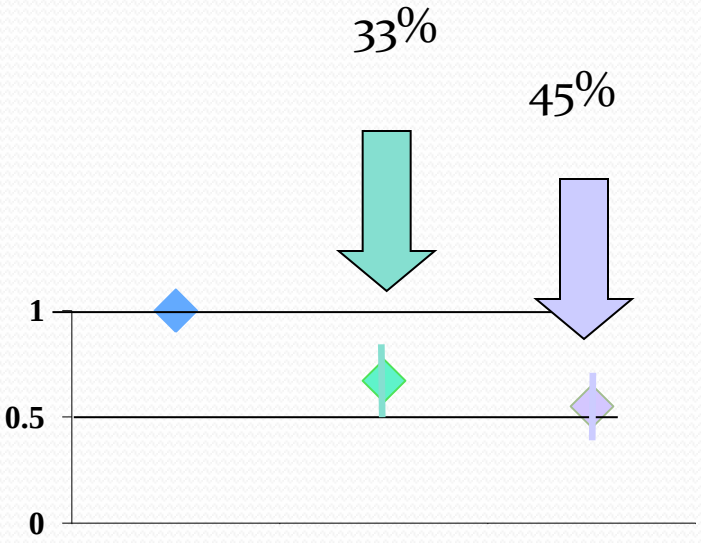
Primary Endpoint:

Adenoma detected at any post-randomization colonoscopy

Detection of any adenoma on follow-up colonoscopy



*p<0.0001 compared to placebo



All patients
Risk Ratio (95% CI)

Bertagnolli, Hawk, Eagle NEJM 2006

Secondary Analysis for APC

Outcome: Number of adenomas detected by colonoscopy

- Objectives

  Compare treatments

  Predict adenoma counts at follow-up

- Covariates of interest:

  Treatment

  Number of adenomas at baseline

  Year of surveillance colonoscopy

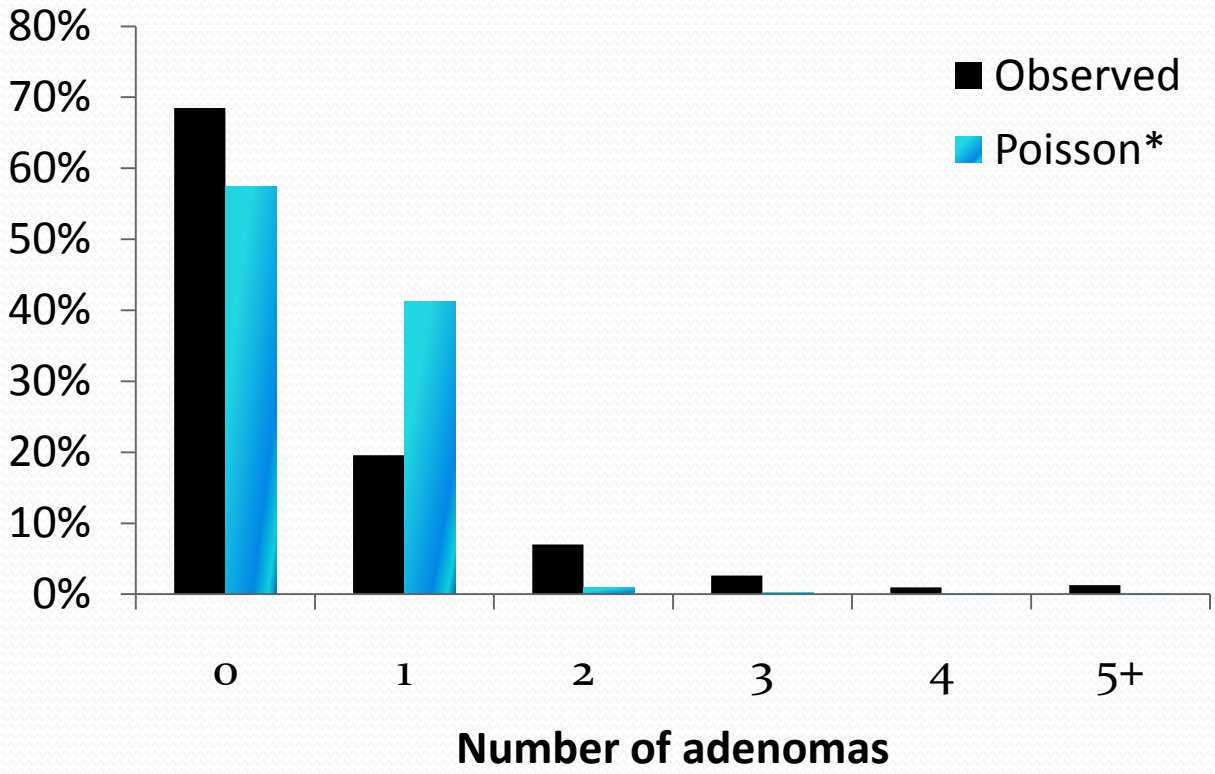
Model considerations:

- 2 follow-up observations per patient
- ➢ Poisson with random effect

Observed Adenoma Counts Post-randomization

	Year 1	Year 3	Overall
No. of adenomas	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**
0	1228 (67.4%)	1075 (69.8%)	2303 (68.5%)
1	372 (20.4%)	287 (18.6%)	659 (19.6%)
2	125 (6.9%)	111 (7.2%)	236 (7.0%)
3	52 (2.9%)	36 (2.3%)	88(2.6%)
4	16 (0.9%)	17 (1.1%)	33 (1.0%)
5+	29 (1.6%)	15 (1.0%)	44 (1.3%)

Predicted Poisson counts compared to observed



* Poisson model of treatment +year + baseline count + random effect

- Poisson is a poor fit of the data

Zero-inflated Poisson (ZIP) model with random effects

$$\Pr(y_{ij}) = (1-\pi_{ij})\, f(y_{ij}) + I(y_{ij}=0)\pi_{ij} \qquad \text{where} \quad f(y_{ij}) = \frac{e^{-\lambda_{ij}}\lambda_{ij}^{\,y_{ij}}}{y_{ij}!}$$

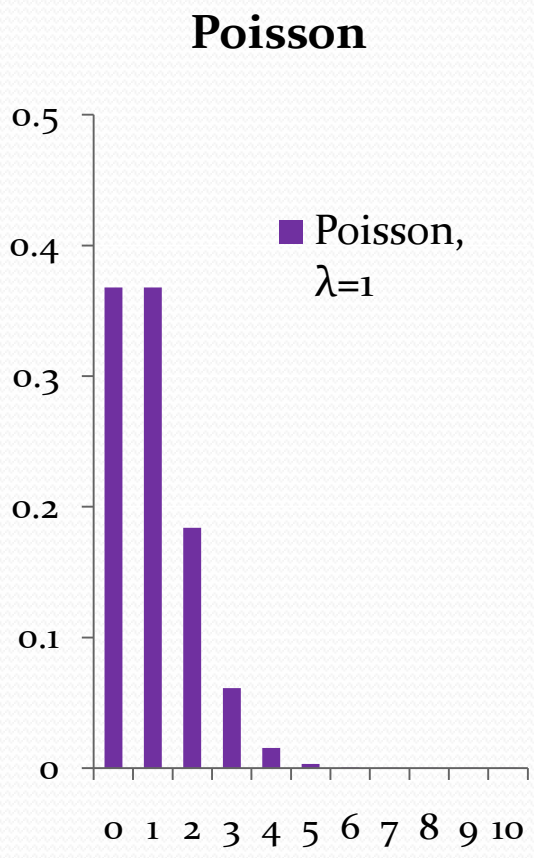
$$\begin{cases} \text{when } y = 0, & \pi_{ij} + (1-\pi_{ij})e^{-\lambda_{ij}} \\ \text{when } y > 0, & (1-\pi_{ij})\dfrac{e^{-\lambda_{ij}}\lambda_{ij}^{\,y_{ij}}}{y_{ij}!} \end{cases}$$

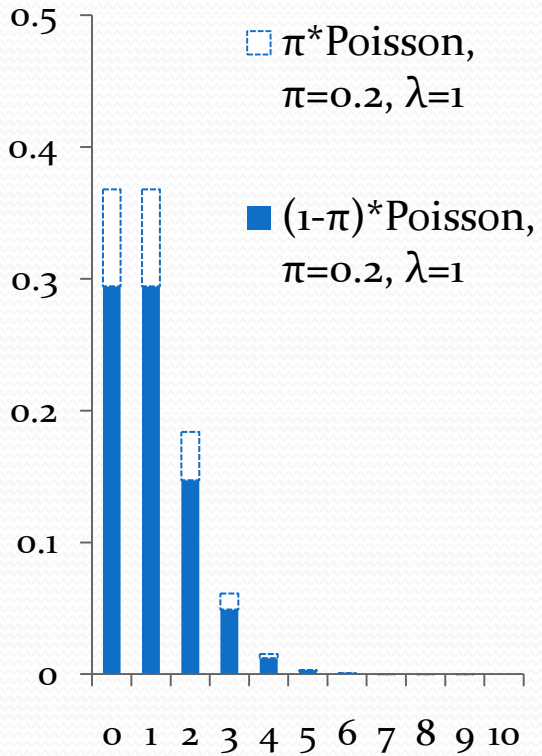
are modeled with

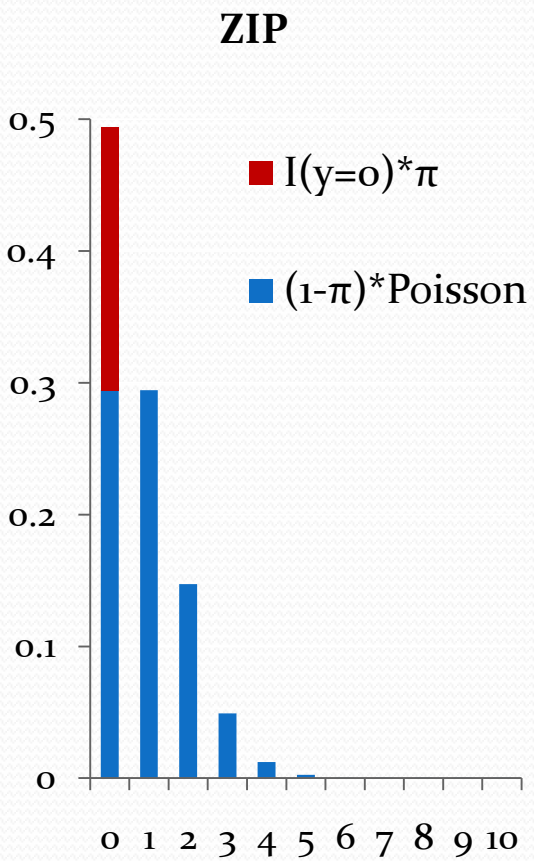
$$Logit(\pi_{ij}) = \boldsymbol{\gamma}'\mathbf{w}_{ij} + \upsilon_i$$
$$Log(\lambda_{ij}) = \boldsymbol{\beta}'\mathbf{x}_{ij} + \nu_i$$

y_{ij} response variable for the j^{th} colonoscopy of the i^{th} individual
$\boldsymbol{x}_{ij}$ and $\boldsymbol{w}_{ij}$ are the vector of known covariates for Poisson and logistic
$\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ are the Poisson and logistic regression parameters
π_{ij} is a mixing parameter for the mixture of a binary and a Poisson process
υ_i and ν_i are random effects assumed to be $\upsilon_i \sim N(0, \sigma_1^2)$ and $\nu_i \sim N(0, \sigma_2^2)$

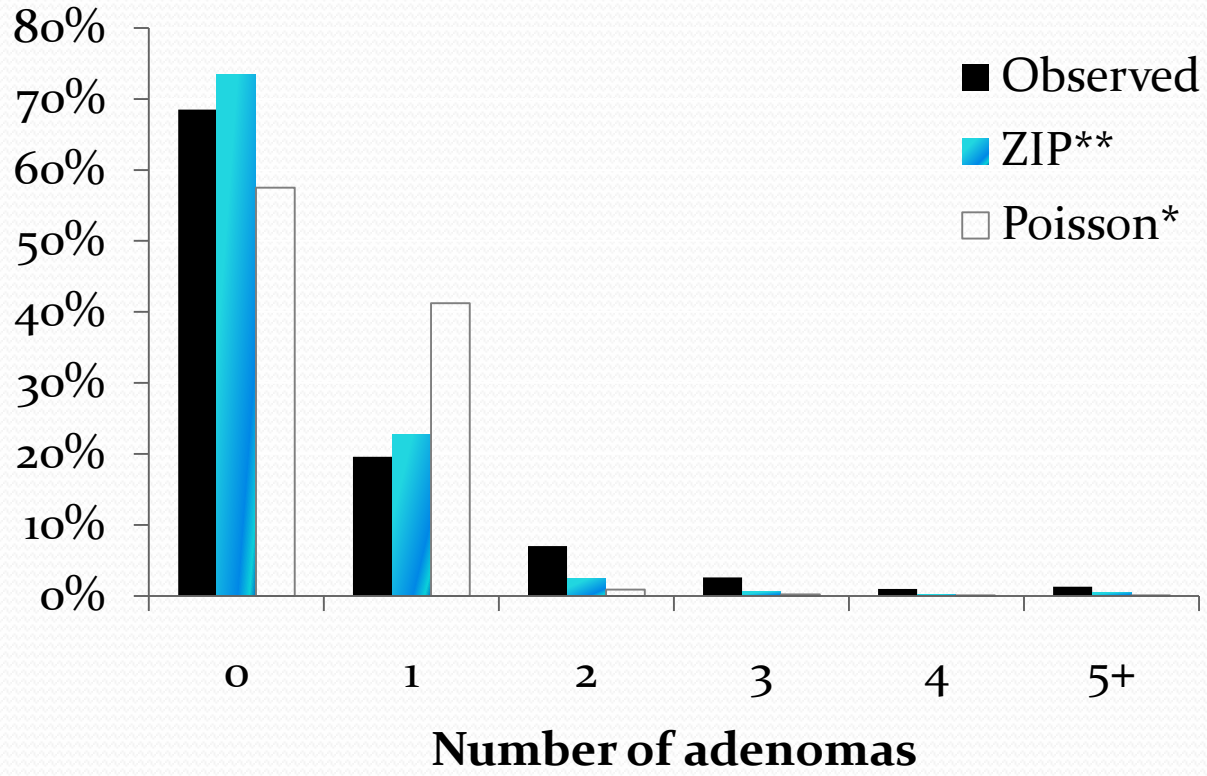
How ZIP can better fit our data







ZIP predicted counts versus observed



*Poisson model of treatment +year + baseline count + random effect

**ZIP model with the same covariates in both submodels

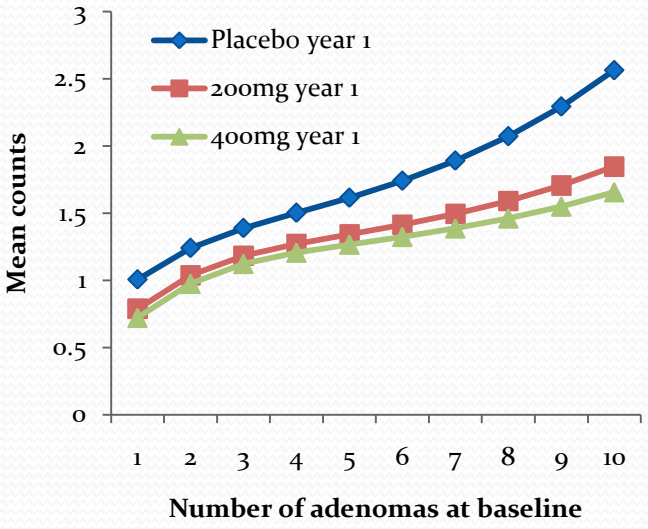
- ZIP model fits the observed data better than the Poisson

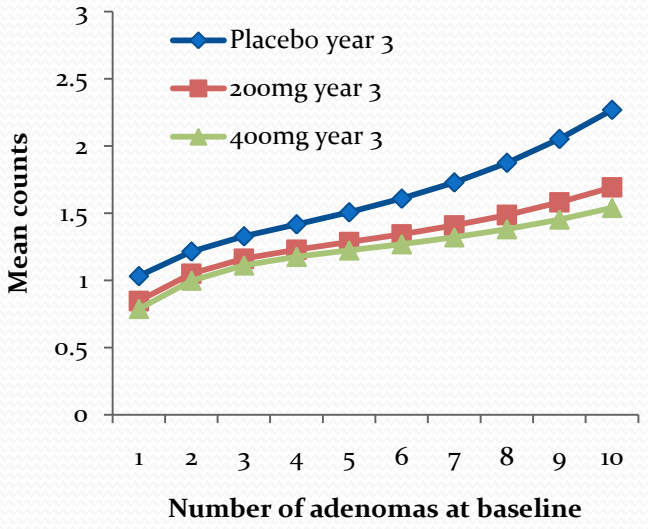
Parameter Estimates of ZIP with random effects model

Table 1: Zero-inflated Poisson model regressing number of adenomas upon all variables shown

	Logistic (γ)			Poisson (β)		
Variables	Estimate	SE	p-value	Estimate	SE	p-value
Intercept	0.115	0.57	0.84	-0.724	0.12	<.0001
200 mg (vs placebo)	-0.495	0.52	0.34	-0.512	0.11	<.0001
400 mg (vs placebo)	-0.655	0.6	0.27	-0.732	0.13	<.0001
year 3 (vs year 1)	0.323	0.39	0.41	-0.172	0.06	0.007
# adenomas at baseline	1.08	0.27	<.0001	0.156	0.02	<.0001

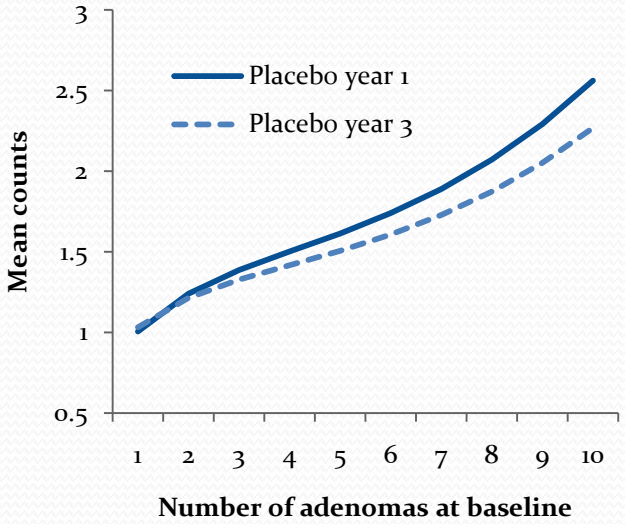
Estimated mean adenoma counts

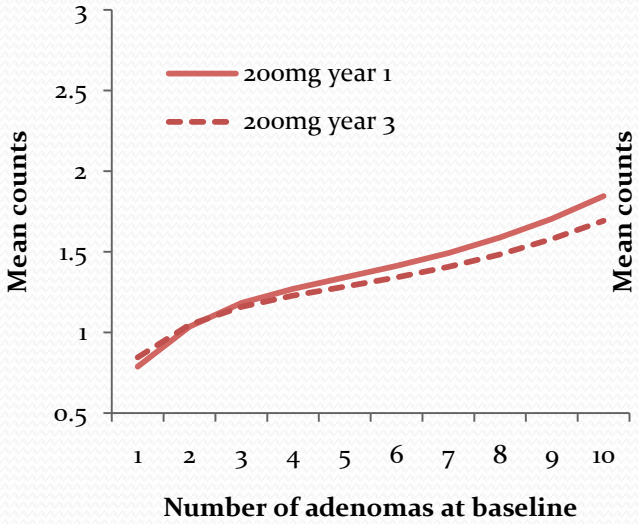


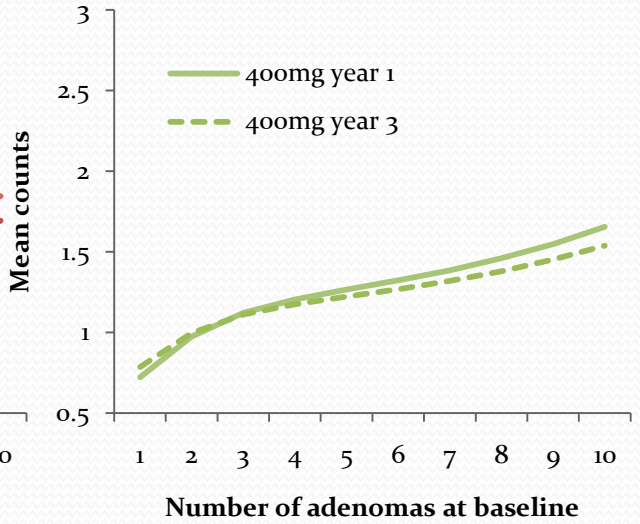


- Mean adenoma count is consistently lower on celecoxib than placebo (p<.0001)
- Mean adenoma count increases with increasing number of adenomas at baseline (p<.0001)

Estimated mean adenoma counts







- Year 3 colonoscopy overall has lower estimated mean counts than year 1 (p=0.03)

Conclusions

- ZIP with random effects demonstrates a better model fit of the data than the Poisson model
- Parameter estimates from ZIP do not have direct clinical interpretation, however the model is still clinically relevant

- Celecoxib significantly reduces expected adenoma count in a dose-dependent manner, compared to placebo
- Baseline adenoma count is significantly associated with the number of adenomas detected at follow-up
- Expected adenoma count at year 3 is also significantly lower than at year 1

References

APC trial results:

Bertagnolli MM, Eagle CJ, Zauber AG, et al. A randomized trial of celecoxib to prevent sporadic colorectal adenomas. N Engl J Med 2006; 355:873-84

Bertagnolli MM, Eagle CJ, Zauber AG, et al. Five-Year Efficacy and Safety Analysis of the Adenoma Prevention with Celecoxib Trial. Cancer Prev Res; 2009; 2(4): 310-21

ZIP with random effects papers:

Hall DB. Zero-inflated Poisson and Binomial Regression with Random Effects: A Case Study. Biometrics; 2000; 56:1030-1039

Yau KK and Lee AH. Zero-inflated Poisson regression with random effects to evaluate occupational injury prevention programme. Statist Med; 2001; 20:2907-2920

Analysis using SAS:

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