FEBUXOSTAT:

Should we **g'out** the champagne?

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Gout

“The king of diseases and the disease of kings.”

Lancet 2010; 375: 318–28

Hippocrates Aphorisms of Gout

1. *In gouty affections, inflammation subsides within 40 days*
2. *A woman does not take the gout, unless her menses be stopped*
3. *A youth does not get gout before sexual intercourse*
4. *Gouty affections become active in spring and in autumn*
5. *Eunuchs do not take gout, nor become bald*

Arthritis Research & Therapy 2006, 8(Suppl 1):S1

"...the deposited ***urate*** *of soda* may be looked upon as the cause, and not the effect, of the gouty inflammation" - **Sir Alfred Garrod, 1859**

- 5-year risk of gout
  - UA < 415 umol/L = 0.6%
  - UA > 595 umol/L = 30.5%
- No trial on titration of therapy to UA level
  - Hyperuricemia not always causal

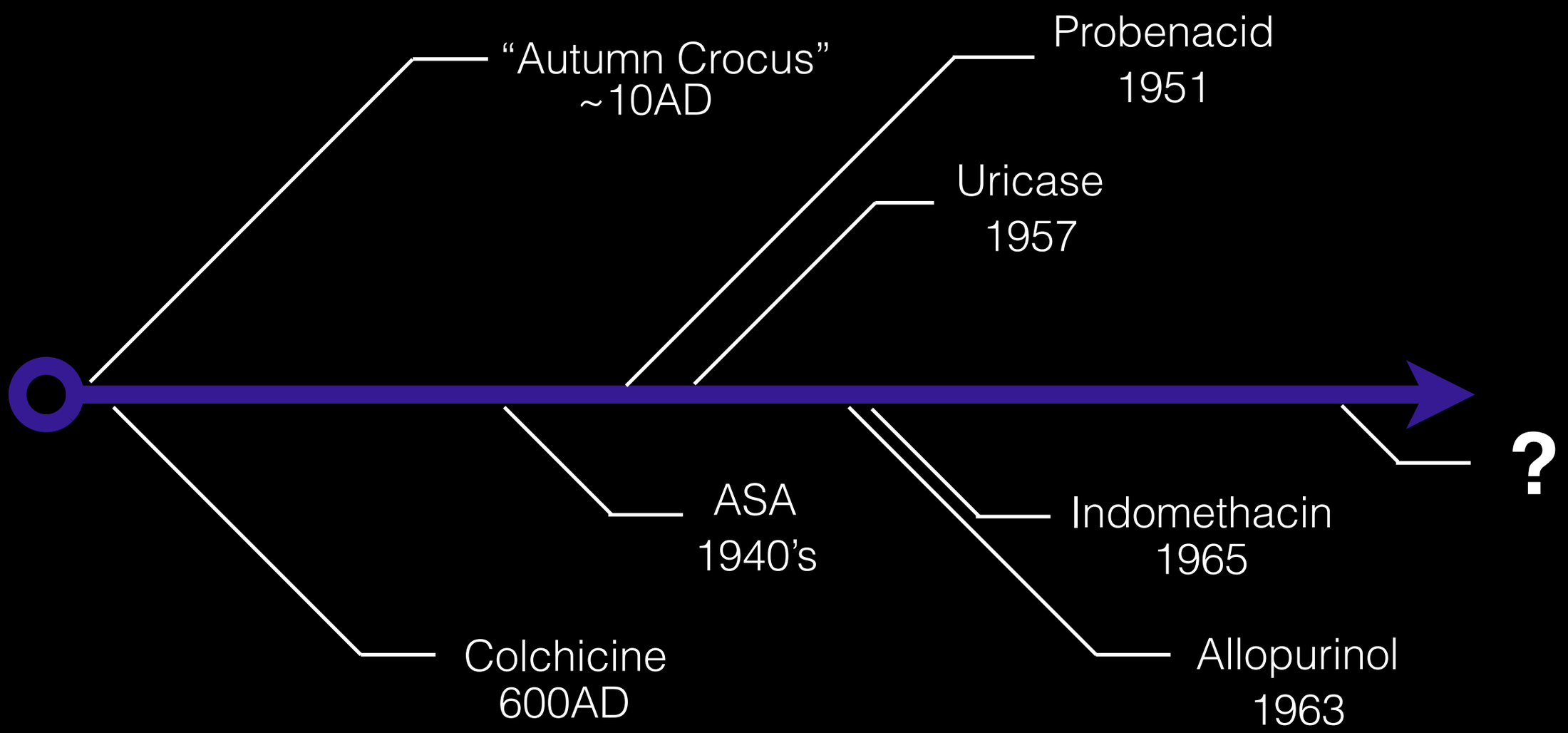
Am J Med 1987;82:421–426.

JAMA 1994;271:302–303

JAMA. 2003;289(21):2857-2860

The Gout, James Gilray, 1799

Pharmacotherapy

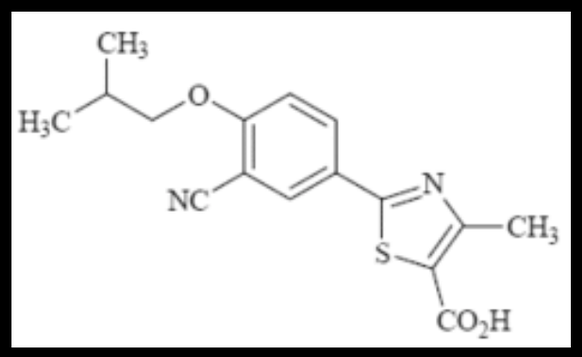


SA Fam Pract 2009;51(5):396-398

Arthritis Research & Therapy 2006, 8(Suppl 1):S1

Limitations of gout therapy

- Narrow therapeutic window
- Concomitant drug interactions
- Patients with renal dysfunction
- Long term adverse effects



Febuxostat

- Approved by Health Canada in 2010
- Non-purine xanthine oxidase inhibitor
- Inhibits both oxidized and reduced forms of xanthine oxidase (vs. allopurinol only reduced)
- Extensively metabolized to weak metabolites
- Very limited renal elimination

CPS Product Monograph 2010

Clinical Question

P	In adult patients with gout...
I	...does febuxostat...
C	...compared to standard therapy (allopurinol/colchicine/indomethacin)...
O	...improve *outcomes*?

Outcomes

Morbidity	*ED visits, hospitalizations*
Reduce/eliminate signs & symptoms	*Reduce pain, # of inflamed joints/tophi*
Modify risk of recurrence	*Reduce frequency of gout flare-up*
Normalize lab value	*Serum/joint uric acid levels*

Search Strategy

- Search terms
  - Febuxostat, uric acid, urate inhibitor, antagnonist/ blocker/ inhibitor, allopurinol, purine, tophus
  - Gout, gouty arthritis, hyperuricemia
- Search engines
  - Google, MEDLINE, EMBASE, IPA
  - ClinicalTrials.org
- Limits
  - English, Human, Adults, Active Comparator RCT, Phase III trials

Results

Short term ≤ 1 year	FACT APEX CONFIRMS
Long term > 1 year	EXCEL

ORIGINAL ARTICLE

Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout

Michael A. Becker, M.D., H. Ralph Schumacher, Jr., M.D., Robert L. Wortmann, M.D., Patricia A. MacDonald, B.S.N., N.P., Denise Eustace, B.A., William A. Palo, M.S., Janet Streit, M.S., and Nancy Joseph-Ridge, M.D.

Effects of Febuxostat Versus Allopurinol and Placebo in Reducing Serum Urate in Subjects With Hyperuricemia and Gout: A 28-Week, Phase III, Randomized, Double-Blind, Parallel-Group Trial

H. RALPH SCHUMACHER, JR.,[1] MICHAEL A. BECKER,[2] ROBERT L. WORTMANN,[3] PATRICIA A. MACDONALD,[4] BARBARA HUNT,[4] JANET STREIT,[4] CHRISTOPHER LADEMACHER,[4] AND NANCY JOSEPH-RIDGE[4]

Clinical Efficacy and Safety of Successful Longterm Urate Lowering with Febuxostat or Allopurinol in Subjects with Gout

MICHAEL A. BECKER, H. RALPH SCHUMACHER, PATRICIA A. MacDONALD, ERIC LLOYD, and CHRISTOPHER LADEMACHER

RESEARCH ARTICLE Open Access

The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial

Michael A Becker*[1], H Ralph Schumacher[2], Luis R Espinoza[3], Alvin F Wells[4], Patricia MacDonald[5], Eric Lloyd[5] and Christopher Lademacher[6]

Study Design (FACT/APEX)

Design	Phase III, multiple arm, MC (US & Canada), DB, randomized, active-controlled trial; Non-inferiority Trials (with superiority analysis if NIF shown)			
P	**Inclusion**: UA >480umol/L + ACR preliminary criteria for gout **Exclusion**: SCr >133 or CrCl <50 ml/min*, BMI >50, liver dz, drug intxns			
I	Febuxostat 80mg & 120 mg (& 240 mg in APEX) PO daily			
C	Allopurinol 300 mg daily (Δ to 100 mg if CKD in APEX) +/- Placebo			
O	**1°: Uric acid <356umol/L in last 3 monthly visits**	**Δ in UA level from baseline**	**Frequency of flare-ups requiring acute treatment**	**Reduction in total # of tophi**
	Adverse Events / Drop outs			

*APEX allowed inclusion of patients with SCr >133 but <170umol/L

FACT Study

Duration	12 months		
Patients n=762	Age 52 Male 96%, Caucasian 77% Baseline UA 585 umol/L BMI 33		Mean history of gout: 12 years CrCl 50-80 mL/min 35% 25% had tophi history/present
Interventions	Allopurinol 300 mg/day	Febuxostat 80 mg/day	Febuxostat 120 mg/day
Procedures	• Modified ITT; **α** 0.05 maintained with Hochberg's method for NI and superiority • 2 week wash out • Naproxen 250 mg BID or Colchicine 0.6 mg daily given in first 8 weeks post-randomization • Monthly physical + labs		

NEJM 2005;353:2450-61

Study Results: Benefits

Group	1°: Uric acid <356 umol/L (@ last 3 monthly visits)	Δ in UA level from baseline	Frequency of flare-ups requiring acute treatment (wk 1-8)	Tophi reduction
APL 300 mg/day (n=253)	21%	-33%	21%	NS
FBX 80 mg/day (n=256)	53% p<0.001	-45% p<0.001	22%	
FBX 120 mg/day (n=251)	62% p<0.001	-52% p<0.001	36% p<0.05	

NEJM 2005;353:2450-61

Study Results

Group	Any ADR	Diarrhea	Dizziness	Rash	LFT elevation	Withdrawals*
APL 300 mg/ day (n=253)	85%	3%	<1%	2	4	26%
FBX 80 mg/ day (n=256)	80%	3%	2%	<1	4	34%
FBX 120 mg/ day (n=251)	75% p<0.01	3%	1%	<1	5	39%

***Most common reasons for discontinuation: loss-to-f/u, LFT increase, rash**

NEJM 2005;353:2450-61

APEX Study

Duration	7 months				
Patients (n=1072)	Age 52, Male 95%, Caucasian 80% Baseline UA 585 umol/L		Average history of gout: 11 years BMI 33, 62% obese SCr 133-177 umol/L 4%		
Randomization	**Placebo** **1**	**FBX 80 mg/day** **2**	**FBX 120 mg/day** **2**	**FBX 240 mg/day** **1**	
	APL 300 mg/day **2**				
Procedures	• Modified ITT; **α** 0.05 maintained with Hochberg's method for NI and superiority • Allopurinol dosing depended on renal function • 2 week washout if already on therapy then naproxen 250 mg BID or Colcichine 0.6 mg daily given in first 8 weeks post-randomization • Monthly physical + labs				

Arthritis Rheum. 2008; 59(11):1540-8

Study Results

Group	1°: Uric acid <356 umol/L (@ last 3 monthly visits)	Δ in UA level from baseline	Frequency of flare-ups (self-reported) Month 2-7	Reduction of palpable reduction
Placebo (n=134)	0%	-3%	20%	NS
APL 300 mg/day (n=268)	22%	-34%	23%	
FBX 80 mg/day (n=267)	48% p<0.001	-45% p<0.05	28%	
FBX 120 mg/day (n=269)	65% p<0.001	-52% p<0.05	36% p<0.05	
FBX 240 mg/day (n=134)	69% p<0.001	-66% p<0.05	46% p<0.05	

Arthritis Rheum. 2008; 59(11):1540-8

Study Results: ADRs

Group	Any ADR	Diarrhea	Dizziness	Rash	LFT elevation	Withdrawals*	CV Events
Placebo (n=134)	72%	8%	2%	5%	6%	25%	0
APL 300 mg/ day (n=268)	75%	6%	1%	5%	2%	22%	1
FBX 80 mg/day (n=267)	68%	6%	2%	5%	6%	35%	5
FBX 120 mg/ day (n=269)	68%	7%	2%	6%	4%	26%	5
FBX 240 mg/ day (n=134)	73%	13% p<0.05	7% p<0.05	4%	4%	36%	1

***Most common reasons for withdrawals: loss-to-f/u, adverse events, gout flares**

Arthritis Rheum. 2008; 59(11):1540-8

Critique & Applicability

- Internal validity:
  - Short study periods & high loss-to-followup rates
  - Allopurinol dosing
- Generalizability:
  - Surrogate outcomes driven
  - Renal patients & drug interactions
- Concerns:
  - CV events signal?

CONFIRMS Study

Design	MC, DB, Non-inferiority RCT x 26 weeks 30 day washout period if on previous UA therapy		
Patients n=2269	**Inclusion**: ARA criteria for gout, SCr <177 umol/L, UA >475 umol/L **Exclusion**: BMI >50, liver disease, elevated AST/ALT, CrCl <30 ml/min	**Age:** 53 **Male:** 95% **Caucasian:** 82% **Baseline UA:** 571 umol/L **Average history of gout**: 11 years **BMI:** 33, **CrCl of 30-59 mL/min:** 17%	
Interventions	Allopurinol 300 mg/day	Febuxostat 40 mg/day	Febuxostat 80 mg/day
Procedures	• Modified ITT analysis; multiplicity adjustment? • Allopurinol dosing depended on renal function (changed to 200 mg/day) • Naproxen 250 mg BID or Colcichine 0.6 mg daily given in first 8 weeks post-randomization • Monthly physical + labs		

Arthritis Research & Therapy 2010, 12:R63

Study Results

Group	1°: Uric acid <356umol/L (@ final visit)	Δ in UA level from baseline	Frequency of flare-ups requiring acute treatment	Tophi
APL 300mg/day (n=755)	42%	-31.3%	25%	Not reported
FBX 40mg/day (n=757)	45%	-33.1%	31%	
FBX 80mg/day (n=756)	67% p<0.001	-40.6% p<0.001	31%	

Arthritis Research & Therapy 2010, 12:R63

Study Results: ADRs

Group	Any ADR	Diarrhea	Dizziness	Rash	LFT elevation	Withdrawals*	CV Events**
APL 300mg/ day (n=755)	57.3%	7.5%	?	7.3%	6.6%	18%	3
FBX 40mg/ day (n=757)	56.7%	5.9%	?	5.8%	8.3%	17%	0
FBX 80mg/ day (n=756)	54.2%	6.2%	?	5.6%	6.9%	21%	3

***Most common reasons for withdrawals: loss-to-f/u, adverse events, gout flares**

****APTC definition: CV death, non-fatal MI, non-fatal stroke**

Arthritis Research & Therapy 2010, 12:R63

Critique & Applicability

- Internal validity:
  - Short study but better withdrawal rates!
  - Adjustment for multiplicity?
- Generalizability:
  - Success with surrogate outcomes
  - Renal patients & drug interactions
- Concerns:
  - No increase in CV events...

EXCEL Study

Design	OL, MC, active control extension trial of FACT and APEX x 3 years		
Patients n=735	**Age** 51, ”majority” **male** **Caucasian**: 80%, **Baseline UA**: 585 umol/L	Average history of gout: 11 year BMI 33, mean weight 105kg SCr >133umol/L: 2%	
Interventions	Allopurinol 300mg/day	Febuxostat 80mg/day	Febuxostat 120mg/day
Procedures	• Final visit in FACT and APEX was considered first visit in EXCEL • Re-randomized • Allopurinol dosing depended on renal function • Within first 6 mo, patients on FBX 80mg could switch to 120mg/day if UA >350umol/L and titrate back down; allopurinol group could switch to FBX • If remained >350, treatment was discontinued • Naproxen 250mg BID or Colcichine 0.6mg daily given in first 8 weeks post-randomization • Monthly physical + labs • “modified” ITT analysis		

J Rheumatol 2009;36;1273-1282

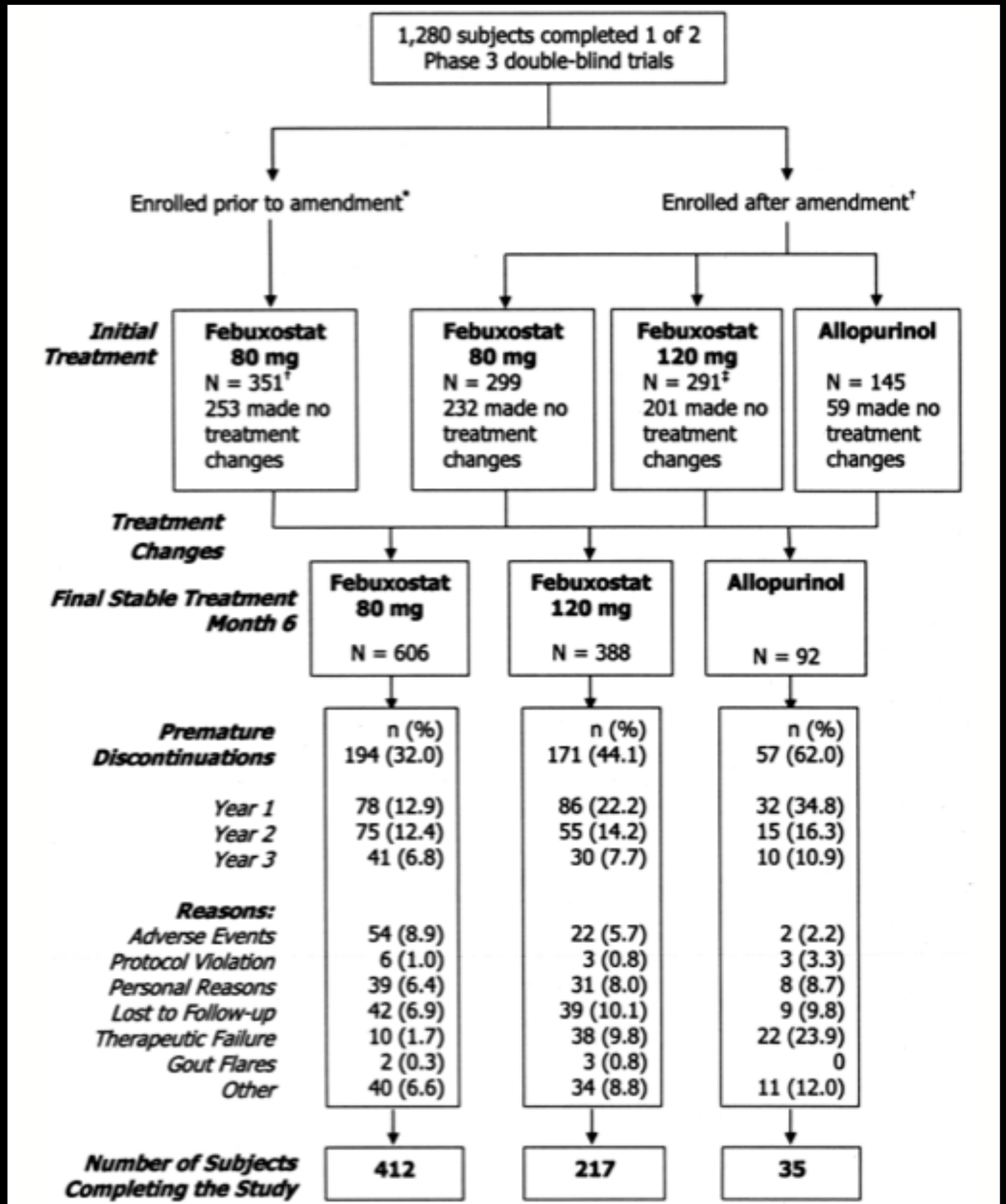


Figure 1. Flow of subjects through the trial. *Subjects could change treatments between febuxostat 80 mg and 120 mg through month 6. †Subjects could change treatments between febuxostat 80 or 120 mg or allopurinol through month 6. ‡One subject assigned to febuxostat 80 mg under initial protocol briefly received febuxostat 120 mg due to investigator error.

EXCEL Study

J Rheumatol 2009;36;1273-1282

Study Results

Group	1°: Uric acid <356umol/L		Δ in UA level from baseline	Frequency of flare-ups requiring acute treatment	Tophi reduction
	@1mo	@1yr			
APL 300mg/day (n=145)	46%	82%	-32%	NS	NS
FBX 80mg/day (n=650)	81%	87%	-47%		
FBX 120mg/day (n=291)	87%	85%	-53%		

J Rheumatol 2009;36;1273-1282

Study Results: ADRs

Group	Any ADR	URTI	MSK	Diarrhea	Withdrawals	CV Events*
APL 300mg/ day (n=145)	245	22	18	2	62%	3
FBX 80mg/ day (n=650)	227	25	13	3	32%	3
FBX 120mg/ day (n=291)	216	23	14	5	44%	2

***Most common reasons for withdrawals: loss-to-f/u, adverse events, therapeutic failures**

ADRs reported as events/100 PY

J Rheumatol 2009;36;1273-1282

Critique & Applicability

- Internal validity:
  - Randomization, group allocation, difficult to ascertain efficacy
  - Analysis: difficult to determine safety
  - High loss to follow-up
- Generalizability:
  - Provides longer term data
  - Information surrounding overall tolerability
- Concerns:
  - Overall CV rates low

Summary of Evidence

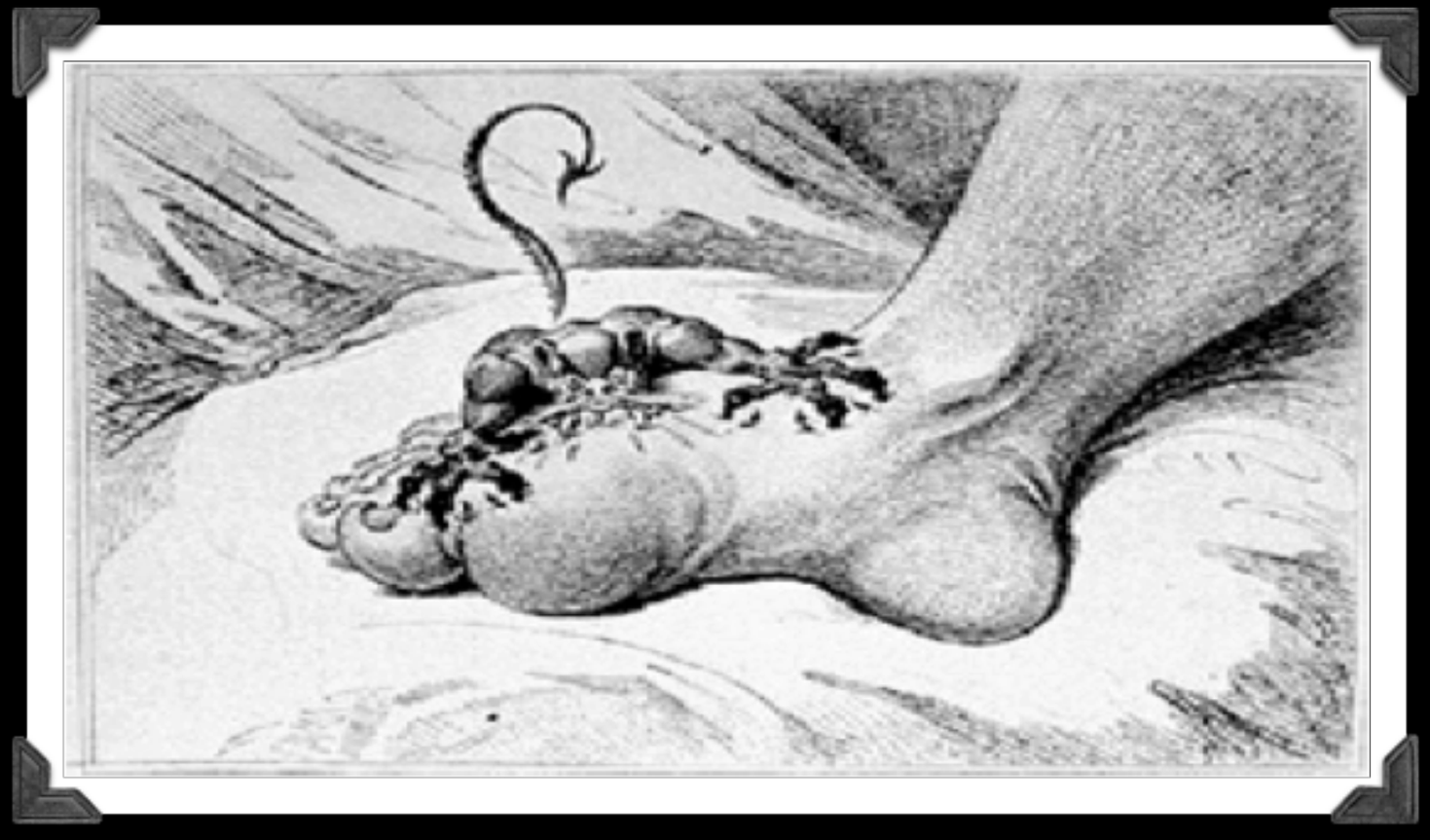
Outcome	Febuxostat (vs allopurinol)
Achieving uric acid <356umol/L	YES
Greater Δ in UA level from baseline	YES
Less frequency of flare-ups	NO?
Tophi reduction	NO?
Adverse events in general	Similar, generally poor tolerability overall
More CV Events	Maybe (CARES trial)

Am Heart J 2012;164:14-20

Key points

- Clinically relevant outcomes
- Surrogate outcomes
- Long-term data? Tolerability?
- Allopurinol still works, well tolerated and low cost
- Patients with renal dysfunction/interacting drugs

Questions?



The Gout, James Gilray, 1799

ACR/EULAR Criteria

A. Presence of characteristic urate crystals in the joint fluid, **or**

B. Presence of a tophus proven to contain urate crystals by chemical means or polarized light microscopy, **or**

C. Presence of **six of the following** clinical, laboratory, and radiographic phenomena:

1. More than one attack of acute arthritis.
2. Development of maximal inflammation within 1 day.
3. Attack of monarticular arthritis.
4. Observation of joint redness.
5. Pain or swelling in first metatarsophalangeal joint.
6. Unilateral attack involving first metatarsophalangeal joint.
7. Unilateral attack involving tarsal joint.
8. Suspected tophus.
9. Hyperuricemia.
10. Asymmetric swelling within a joint on x-ray.
11. Subcortical cysts without erosions on x-ray.
12. Negative culture of joint fluid for microorganisms during attack of joint inflammation.

Arthritis Rheum. 1977; 20(3):895-900

Non-inferiority margin E.g. 10%

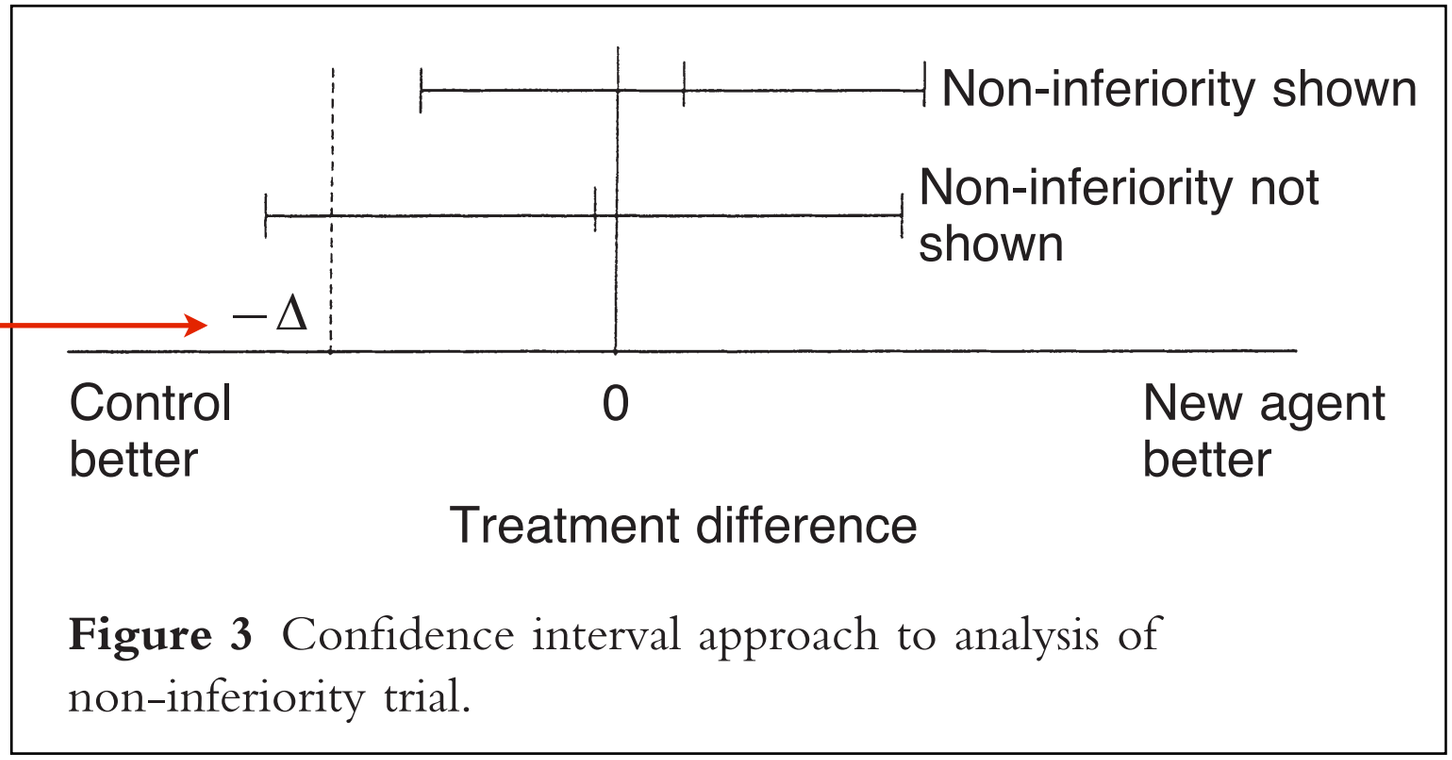


Figure 3 Confidence interval approach to analysis of non-inferiority trial.

Confidence Interval excludes treatment difference of "zero"

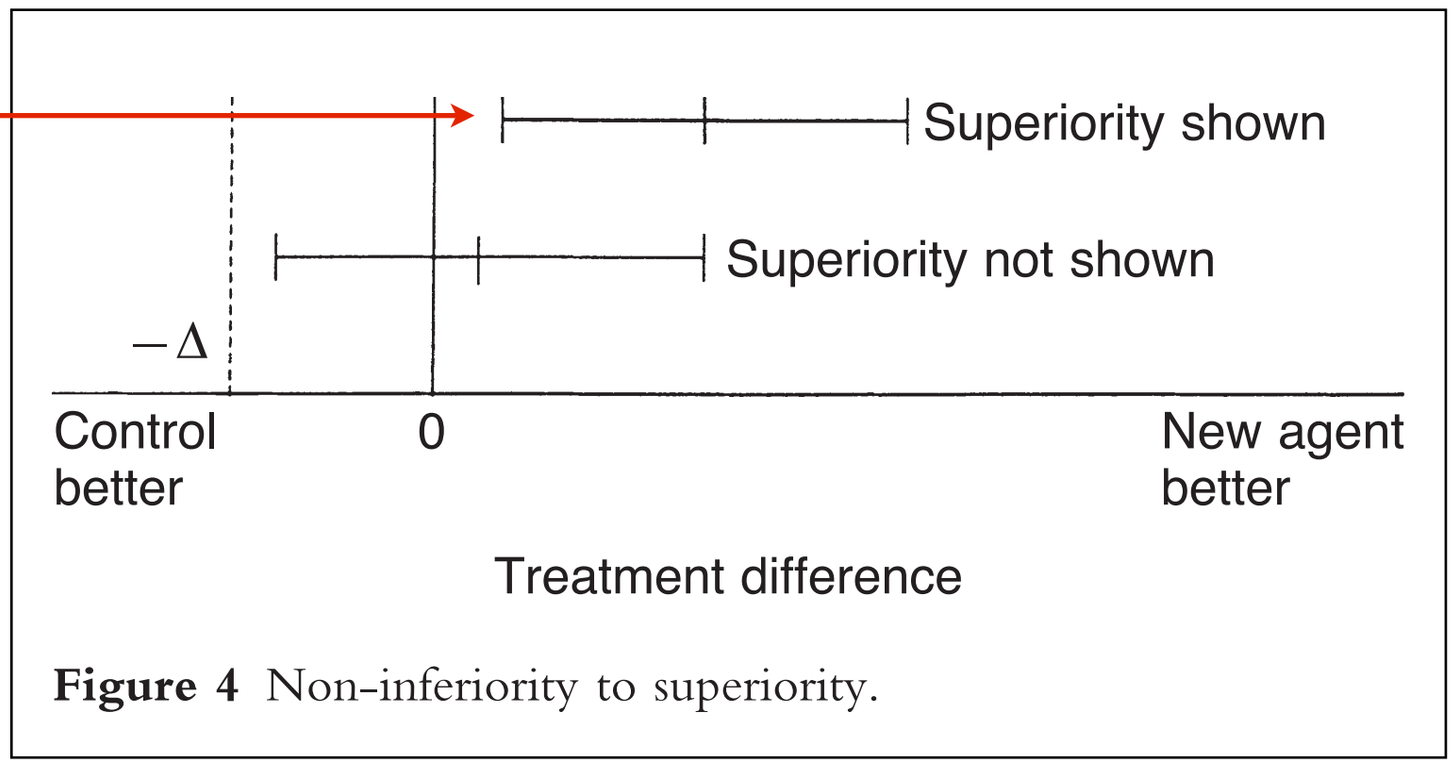


Figure 4 Non-inferiority to superiority.

Br J Clin Pharmacol, 52, 223±228

Adverse Effects

- From actual trial