Optimizing the treatment of IBD through use of therapeutic drug monitoring

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Conflict of Interest Disclosure

Adam S. Cheifetz

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Company	Relationship	Content Area
Janssen	Consulting	IBD
Abbvie	Consulting	IBD
Takeda	Consulting	IBD
Pfizer	Consulting	IBD
Miraca	Consulting/Research	IBD
Ferring	Consulting	GI / preps
AMAG	Consulting	Iron deficiency

Goals

1) Review how we can optimize the use of biologics
2) Describe the role of therapeutic drug concentration monitoring (TDM) with biologics
3) Discuss reactive vs. TDM
4) Learn potential benefits for proactive TDM

Optimizing the Treatment of IBD

- Treat deeper (mucosal healing)
- Treat earlier
- Treat more effectively

Optimizing Treatment of IBD

- Optimizing biologics
  - Induction regimen and maintenance dosing
  - Combination therapy with immunomodulator
  - Earlier use of biologics
- Therapeutic drug concentration monitoring (TDM)
  - Reactive testing of drug concentration and antibodies
    - Better directs care and more cost-effective
  - Proactive TDM – improves outcomes and cost-effective

When and why to do TDM?

- Proactive TDM
  - During maintenance
    - Improves clinical scores and markers of inflammation (CRP)
    - Decreases need for rescue therapy
    - Prolongs duration of infliximab with less infliximab discontinuation
    - Decreases IBD-related hospitalizations and surgeries, serious infusions reactions, ATI and treatment failure when compared with reactive TDM
    - Cost-effective
  - Proactive TDM following reactive TDM is better that reactive TDM alone
  - Optimized (biologic) monotherapy
  - When stopping immunomodulator (in combination with anti-TNF)
  - During induction

American Gastroenterological Association (AGA) Guidelines on TDM

Table 3. Summary of Recommendations of the American Gastroenterological Association Clinical Guidelines for Therapeutic Drug Monitoring in Inflammatory Bowel Disease

Statement	Strength of recommendation	Quality of evidence
In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.	Conditional recommendation	Very low quality
Comment: *Table 4 summarizes suggested trough concentration for anti-TNF therapy, for patients with active IBD on maintenance therapy. Of note, there may be a small subset of patients who may still respond by targeting higher target concentrations. Optimal trough concentrations for induction therapy are uncertain.*		
In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring.	No recommendation	Knowledge gap

Feuerstein et al, Gastroenterology 2017

Consensus statement on TDM in IBD by Australian IBD Consensus working group

Statement	Acceptance (%)	EL	RG
Scenarios when TDM of anti-TNF agents should be performed			
1. In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management	100	II	C
2. TDM can inform clinical decision-making in patients with primary nonresponse	100	III2	C
3. TDM should be performed in patients with secondary loss-of-response to guide clinical decision-making	100	I	B
4. TDM should be considered periodically in patients in clinical remission if the results are likely to impact management	90	IV	D
5. Patients maintained in clinical remission in whom a drug holiday is contemplated, are suggested to have TDM along with other investigations to help guide this decision	100	III2	C

- Includes:
  - Proactive TDM at the end of induction
  - Proactive TDM in clinical remission if results are likely to impact management

Mitrev et al, APT 2017

BRIDGe (Rand panel): When should drug concentration and antibody testing be performed?

- **Appropriate to perform testing**
- At the end of induction, primary non-response
- Secondary non-response
- During maintenance, responding
- Restarting after drug holiday (before 2nd infusion)

- **Uncertain to perform testing**
- At the end of induction, in responders

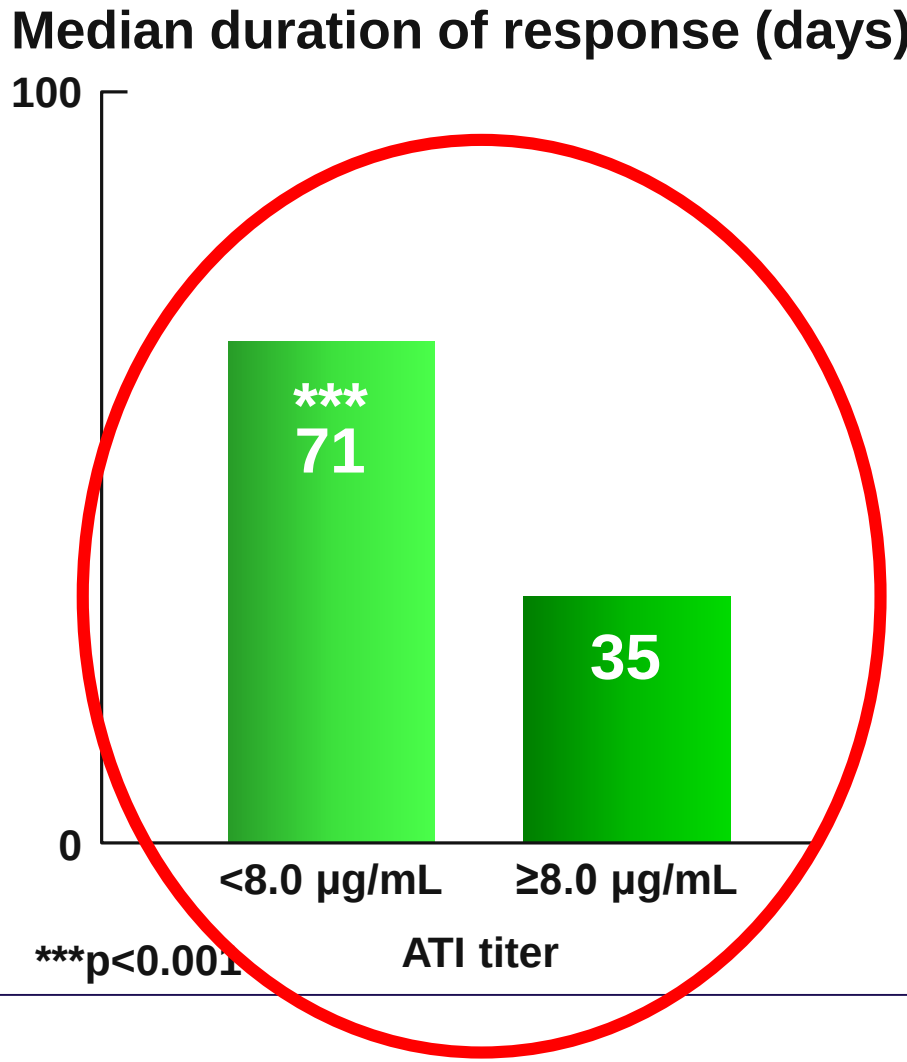
Melmed et al, CGH 2016

www.BRIDGeIBD.com

Episodic therapy is associated with high rates of antibodies to infliximab and shorter duration of response

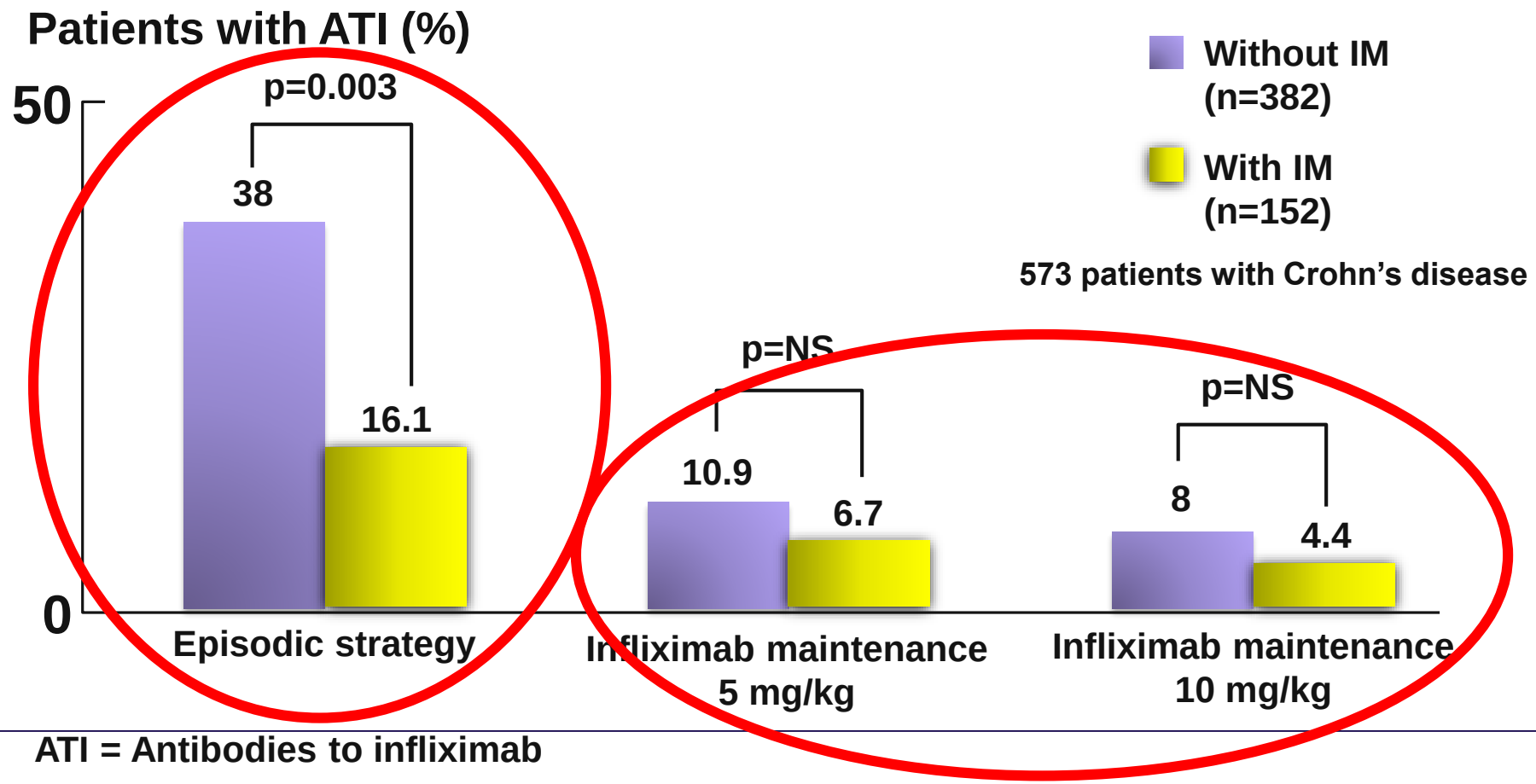
- 125 consecutive refractory CD patients
- On-demand / episodic infliximab treatment, mean 3.9 infusions (range 1–17)
- Antibodies to infliximab (ATI) in 61% patients
- Relative risk of infusion reaction with higher ATI titer: 2.4 (p<0.001)

ATI = Antibodies to infliximab
IFX = infliximab



Baert et al, N Engl J Med 2003:248:601

Immunogenicity of infliximab is decreased with maintenance therapy and combination therapy (ACCENT I)



ATI = Antibodies to infliximab

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Hanauer et al, Clin Gastroenterol Hepatol 2004;2:542

We still haven't fully optimized anti-TNFs

Crohn's disease

Infliximab	Placebo (n=110)	5mg/kg (n=113)	10mg/kg (n=112)
Remission at 30 weeks, %	21	39	45
Median time to LOR, wk	19	38	>54

Adalimumab	Placebo (n=170)	Every other week (n=172)	Weekly (n=157)
Remission at 26 weeks, %	17	40[a]	47[a,b]
Remission at 56 weeks, %	12	36[a]	41[a,b]

Certolizumab pegol	Placebo (n=101)	Certolizumab pegol (n=112)	*P*
Remission at 26 weeks,%	26	42	.01

Sandborn WJ, et al. N Engl J Med. 2007;357(3):228-238.

Colombel JF, et al. *Gastroenterology.* 2007;132(1):52-65.

Non anti-TNF drug concentrations correlate with outcome: *Cohort studies and post-hoc analysis*

Disease	Drug	Concentration	Clinical outcome	Notes
CD (Reinisch CGH 2015)	IFX	>3	Mucosal healing	Post hoc analysis of SONIC
CD (Cornillie GUT 2014)	IFX	> 3.5	Sustained response	Post hoc analysis of ACCENT I
CD (Bortlik JCC 2013)	IFX	> 3	Sustained response	Week 14 or 24 trough
CD (Yarur APT 2017)	IFX	> 10.1	Fistula healing	HMSA
CD (Ward APT 2011)	IFX	> 5.7	Normal FC	ELISA
UC (Papamichael APT 2018)	IFX	> 7.5	Endoscopic healing	>10.5 µg/ml for histologic healing
UC (Adedogun Gastro 2010)	IFX	> 2.4	Clinical response	Post hoc analysis of ACT I and II
CD/UC (Yanai CGH 2015)	IFX	> 3.8	Failed to respond to increase in IFX or change to another anti-TNF	Population was patients with LOR
CD/UC (Ungar CHG 2016)	IFX	> 6.8	Normal CRP	ELISA
CD/UC (Yarur CGH 2015)	IFX	> 8.3	Mucosal healing	HMSA
CD/UC (Roblin IBD 2017)	IFX	> 4.9	Clinical remission, normal CRP and normal FC	Normal FC (<50 mg/g)
CD/UC (Papamichael CGH 2017)	IFX	< 3.5	Treatment failure	<1.8 µg/ml for ATI formation
CD/UC (Brandse IBD 2017)	IFX	< 3	ATI formation	ELISA
CD (Zittan JCC 2016)	ADA	> 8.1	Mucosal healing	HMSA
CD/UC (Ungar CGH 2016)	ADA	> 6.6	Normal CRP	> 7.1 µg/ml for mucosal healing
CD/UC (Roblin CHG 2014)	ADA	> 4.9	Mucosal healing	ELISA
CD/UC (Yarur IBD 2016)	ADA	> 7.8	Histologic remission	HMSA
CD (Vande Casteele APT 2018)	CZP	> 13.8	Normal FC	Pooled data from 9 clinical trials
UC (Adedogun JCC 2017)	GOL	> 1.4	Clinical remission	Post hoc analysis of PURSUIT
CD/UC (Jacoub APT 2018)	VEDO	> 18	Mucosal healing	Week 6 concentrations
CD (Adedogun Gastro 2018)	USTE	> 1.4	Clinical remission	Pooled data from UNITI-1/2 and IM-UNITI

Higher drug concentrations are associated with better outcomes

Undetectable / low drug concentrations are associated with loss of response and antibodies

Factors Affecting the Pharmacokinetics of Monoclonal Antibodies

	Impact on Pharmacokinetics
Presence of anti-drug antibodies	• Decreases serum drug concentration • Threefold-increased clearance • Worse clinical outcomes
Concomitant use of immunomodulator	• Reduces formation of anti-drug Ab • Increases serum drug concentration • Decreases drug clearance • Better clinical outcomes
High baseline TNF	• May decrease serum drug concentration by increasing clearance
Low albumin	• Increases clearance • Worse clinical outcomes
High baseline CRP	• Increases clearance
Body size	• High BMI may increase clearance
Gender	• Males have higher clearance

mAB, monoclonal antibody; ADA, antidrug antibody

Ordas I et al. Clin Pharmacol Ther. 2012;91:635.

Reactive TDM
(Secondary non-response)

- Better directs care
- More cost effective than empiric dose escalation

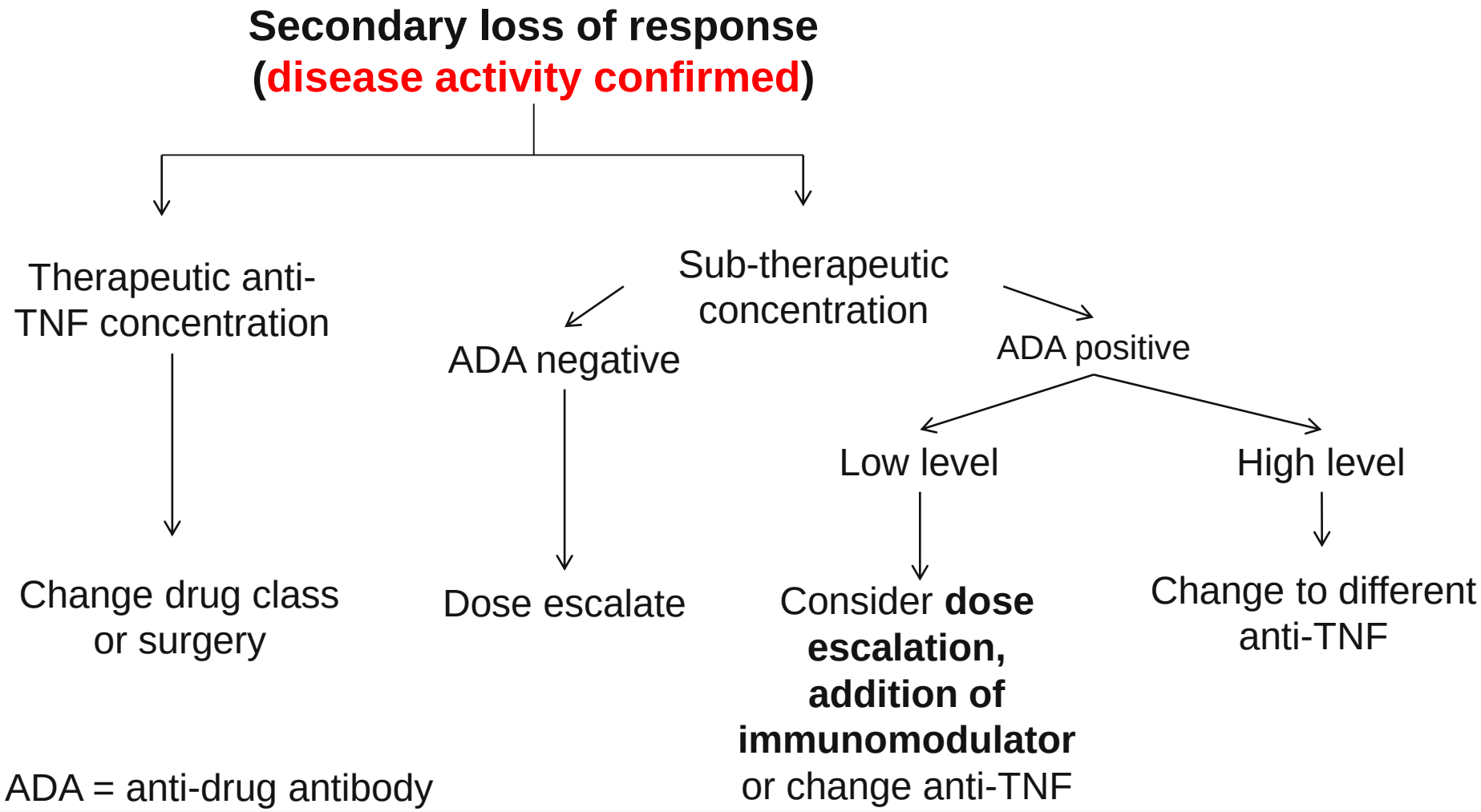
Measurement of IFX Conentration and ATI

Test results impacted treatment in 73% of patients

Subtherapeutic IFX	**Dose escalation**	**Complete or partial response - 86%**
Subtherapeutic IFX	**Switch anti-TNF**	**Response - 33%**
Therapeutic IFX		**No evidence of active inflammation in 62% of the patients**
ATI positive	**Switch anti-TNF**	**Response - 92%**
ATI positive	**Dose escalation**	**Response - 17%**

Afif W, et al. *Am J Gastroenterol.* 2010;105(5):1133-9.

Reactive testing algorithm

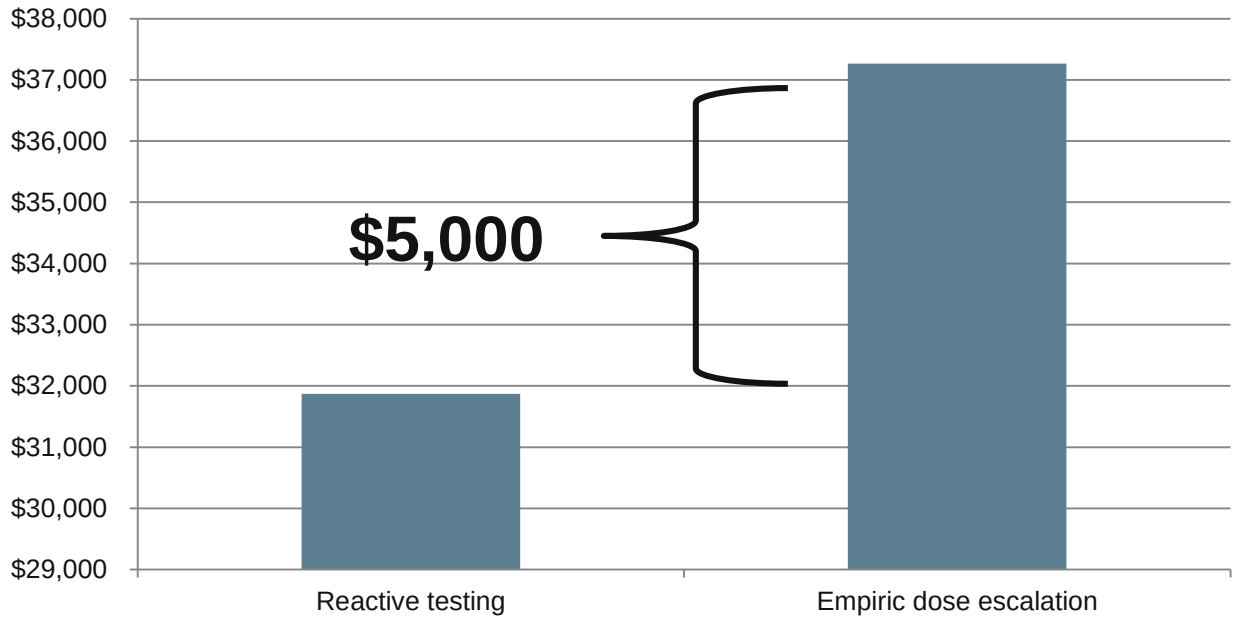


ADA = anti-drug antibody

Adapted from Papamichail and Cheifetz , JCC 2016

Reactive testing is cost effective and more appropriately directs care

- Compared to empiric dose escalation for secondary loss of response[1]
  - Reactive testing yielded similar QALYs
  - Similar rates of remission and response
  - Reactive testing was less expensive
    - Lower use of high-dose biologics
    - Greater time off biologics



[1]Velayos et al. *Clin Gastronetol Hepatol* 2013;11:654-666

Proactive TDM
(During maintenance, responding)

- Improves clinical scores and markers of inflammation (CRP)
- Decreases need for rescue therapy
- Prolongs duration of infliximab with less infliximab discontinuation
- Decreases IBD-related hospitalizations and surgeries, serious infusions reactions, ATI and treatment failure when compared with reactive TDM
- Cost-effective

Vande Casteele et al. Gastroenterolgy 2015
Vaughn B et al. Inflamm Bowel Dis 2014 Nov;20(11):1996-2003

Therapeutic drug monitoring – Proactive monitoring

- Commonly performed in other situations
  - Cyclosporine, tacrolimus in solid organ transplantation
  - Cyclosporine and tacrolimus use in UC
  - Vancomycin and gentamycin in sepsis
- Therapeutic window
  - High concentrations can result in increased toxicity
  - Low concentrations result in lack of efficacy
  - Biologics – low concentrations result in immunogenicity*

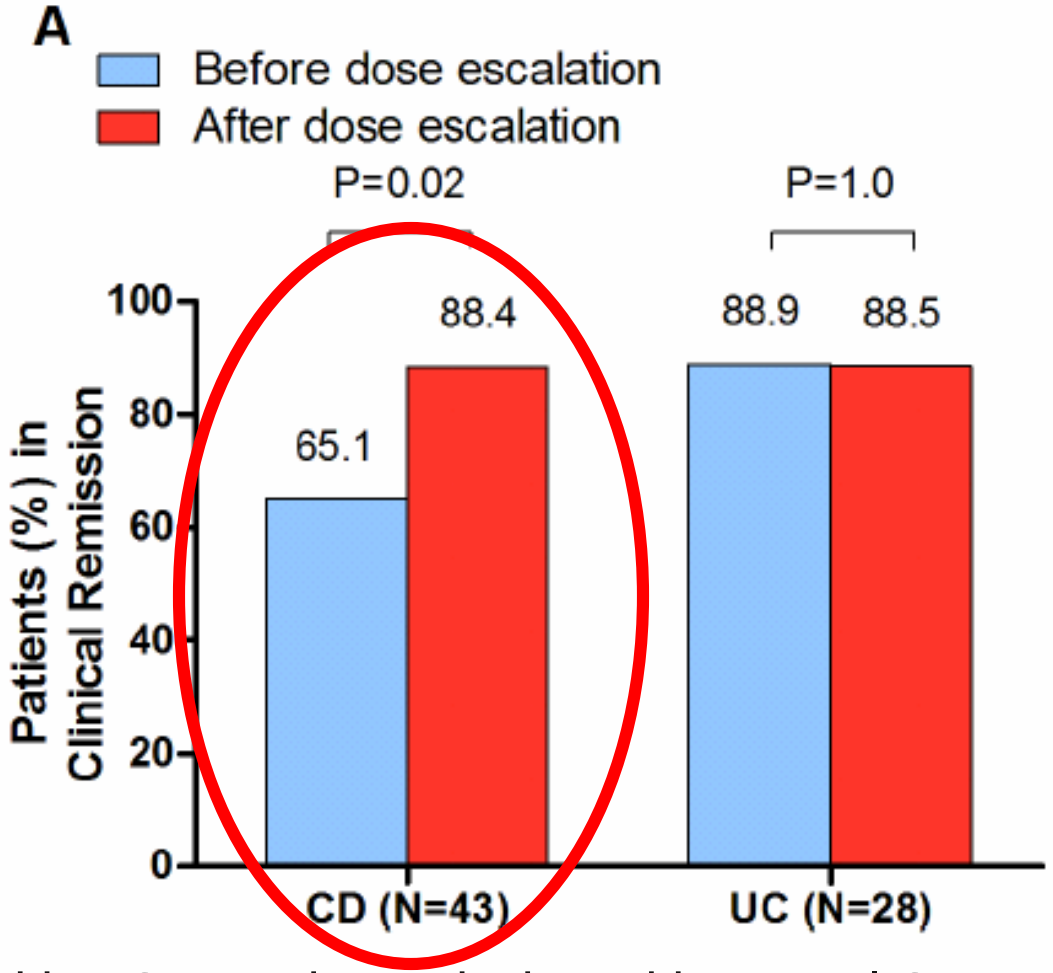
Monchaud C et al. Clin Pharmacokinet 2009;48:419–62
Van Assche G et al. Gastroenterology 2003;125:1025–31.
Ziring DA et al. J Pediatr Gastroenterol Nutr 2007;45:306–11.
Zelenitsky S et al. Int J Antimicrob Agents 2013;41:255–60.
Hansen M et al. Acta Anaesthesiologica Scandinavica 2001;45:734–40.

Proactive testing in IBD: TAXIT

- **T**rough level **A**dapted infli**XI**mab Treatment (**TAXIT**) trial.
- Patients: Infliximab maintenance therapy with stable clinical response
- **All** patients underwent infliximab **dose optimization** to trough level of 3-7ug/ml
- Randomized to:
  - Infliximab dosing based on clinical symptoms and CRP
  - Infliximab dosing based on trough concentration
- Primary outcome: Clinical remission at 1 year

Vande Casteele et al. Gastroenterolgy 2015

Dose escalation for Crohn's improved disease control (symptoms and CRP)



Most patients with UC were in remission with normal CRP

Vande Casteele et al. Gastroenterolgy 2015

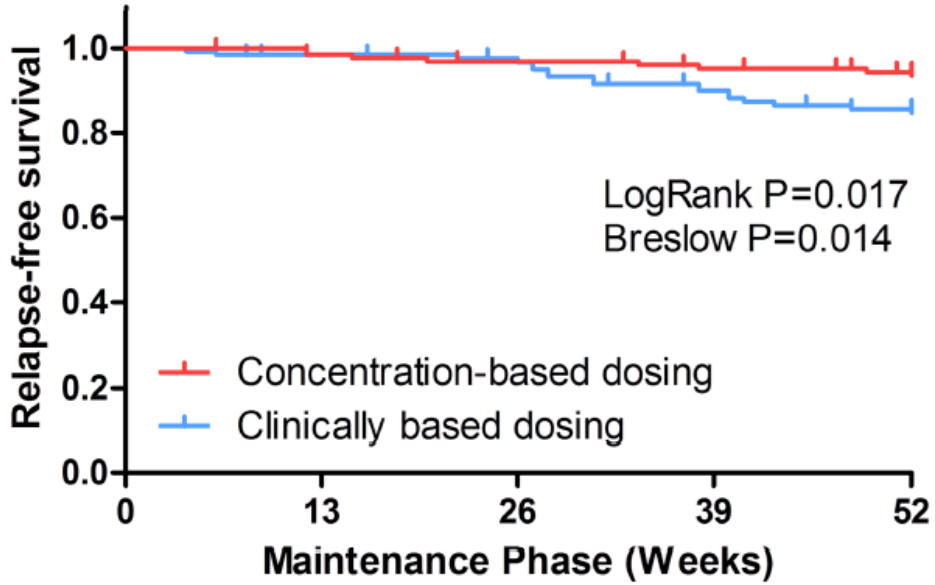
TAXIT: Primary endpoint - 1 year after optimization: No difference in (clinical and biological) remission rates between concentration and clinically dosed groups

Issues:

- All patients were initially optimized
- Only 1 year follow-up
- Sub-therapeutic window

Secondary endpoints favor dosing to infliximab concentration

- **Less patients needed rescue therapy (7% vs. 17.3%; p=0.004)**
- **Less patients had undetectable trough concentrations (OR 3.7; p<0.001)**
- **Similar cost between both groups**
  - ***25% underwent dose de-escalation***

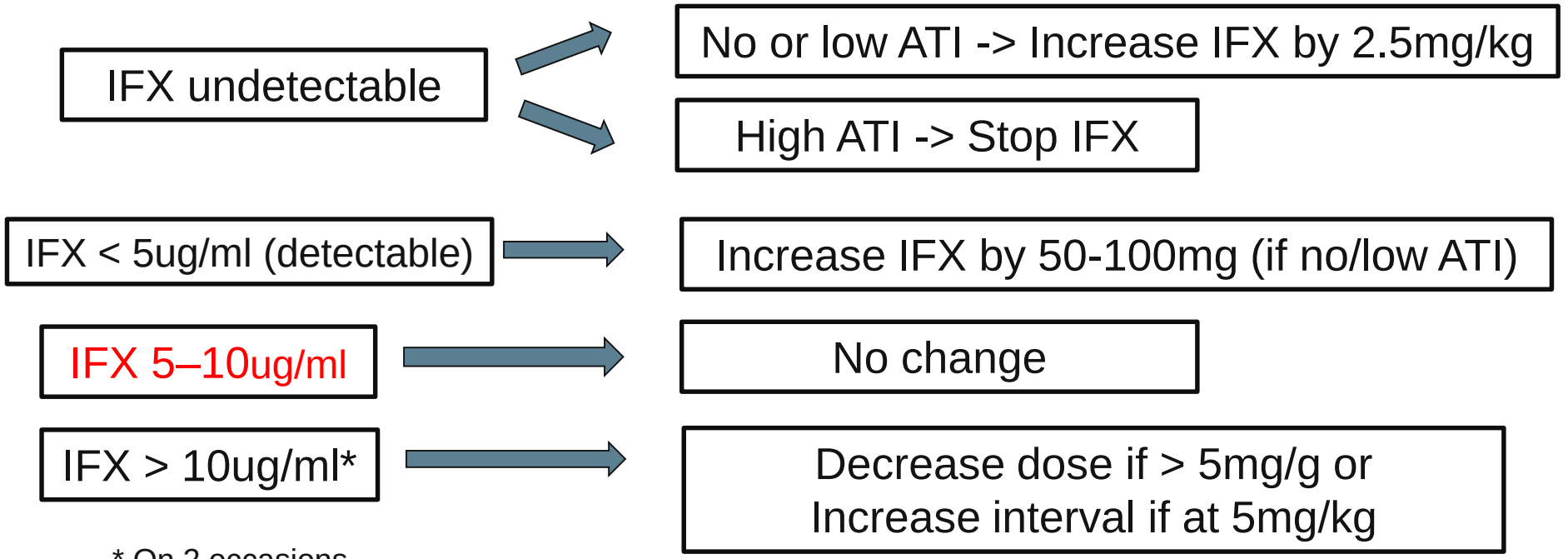


Week	0	13	26	39	52
N at risk	128	127	121	117	111
	123	120	116	107	97

Vande Casteele et al. Gastroenterolgy 2015

Proactive TDM study group

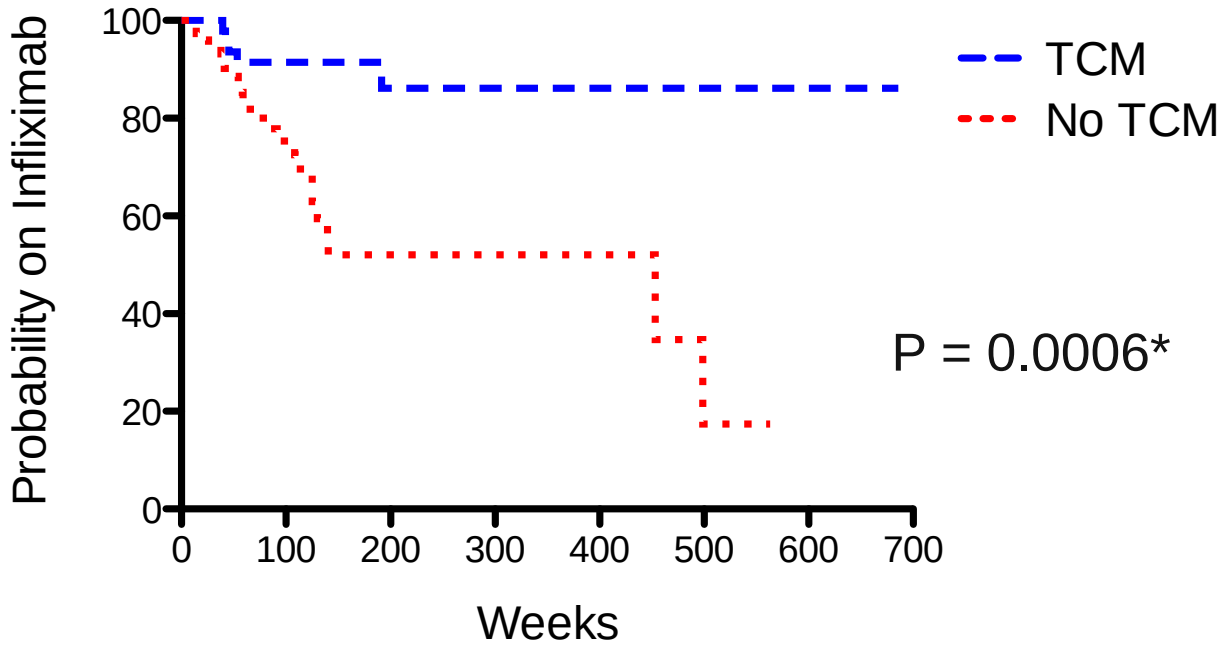
- Retrospective cohort (TDM vs. control)
- Typical protocol for infliximab proactive dose optimization



* On 2 occasions

Vaughn B et al. Inflamm Bowel Dis 2014 Nov;20(11):1996-2003

Proactive therapeutic concentration monitoring and dose optimization results in a longer duration of infliximab and less discontinuation than standard of care

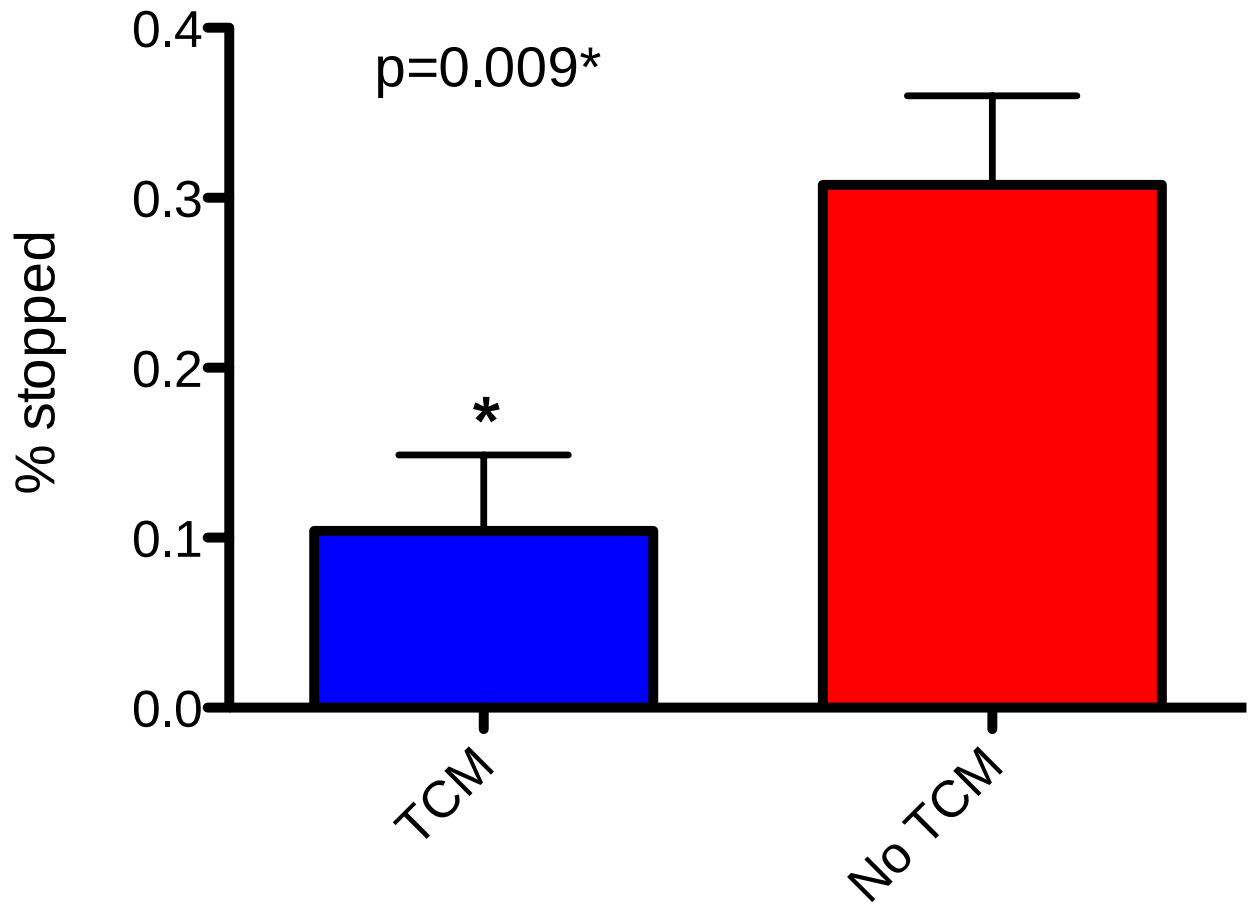


Number at risk

TCM	48	34	16	10	5	4	2
No TCM	78	29	10	5	3	2	

Vaughn B et al. Inflamm Bowel Dis 2014 Nov;20(11):1996-2003

Less infliximab discontinuation in the proactive TDM group



Vaughn B et al. Inflamm Bowel Dis 2014 Nov;20(11):1996-2003

Reasons for infliximab discontinuation

	Optimized	Not Optimized
Ongoing IBD symptoms	0	15
Adverse events		
Pneumonia	0	1
Drug induced lupus	1	0
Psoriasis	1	0
High antibody (ATI) level	1	0
Infusion reactions		
Acute infusion reaction	0	6
Delayed infusion reaction	1	0
Other (unrelated to infliximab)*	1	2

73% of controls underwent dose escalation; ¾ increased IFX 10mg/kg

Median IFX dose increase was 100mg (range 50 - 200mg) in TDM group

14.6% patients in TDM de-escalated therapy (reduced dose or stopped)

*Includes: unable to afford co-payment, surgery for adhesive small bowel obstruction, colectomy for flat LGD.

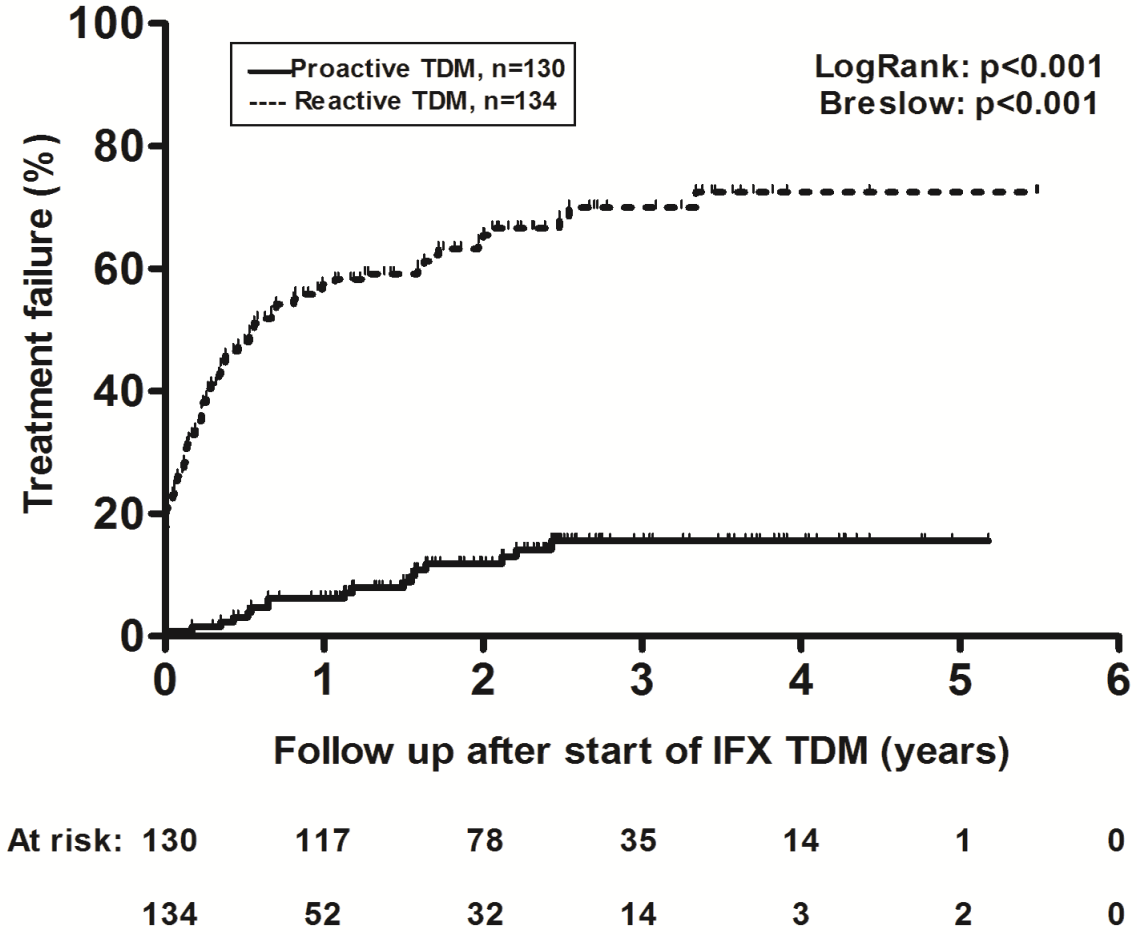
Vaughn B et al. Inflamm Bowel Dis 2014 Nov;20(11):1996-2003

Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab

- Multicenter (BIDMC and UPenn), retrospective, observational study.
- 153 patients with IBD who responded to infliximab and received maintenance therapy and underwent either proactive or reactive TDM, based on the *first* infliximab concentration / antibodies to infliximab (ATI) measurement (Prometheus Labs)
- Outcomes: Treatment failure, IBD-related surgery, hospitalization, antibodies to infliximab (ATI), and serious infusion reaction (SIR)

Papamichael, Chachu, VajraveluVaughn, Ni, Osterman*, Cheifetz* Clinical Gastroenterology and Hepatology 2017

Less Treatment Failure with Proactive TDM



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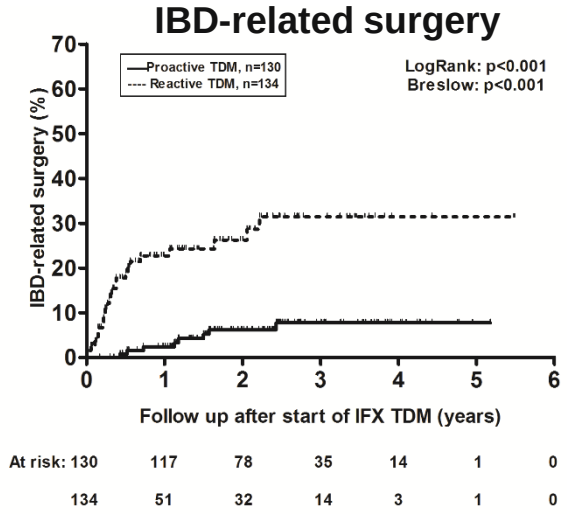
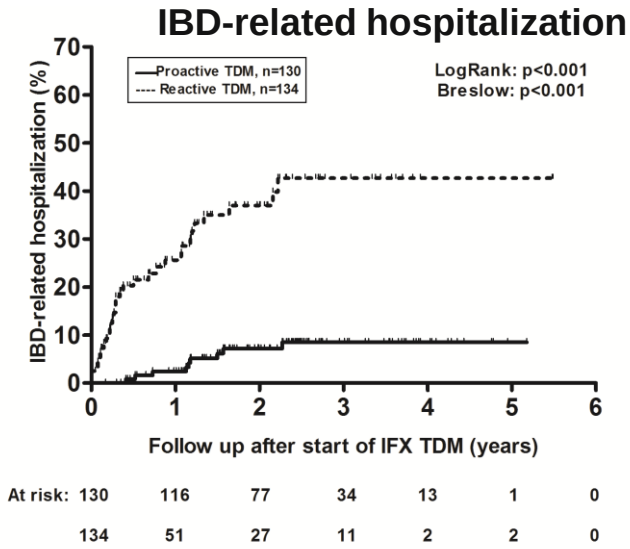
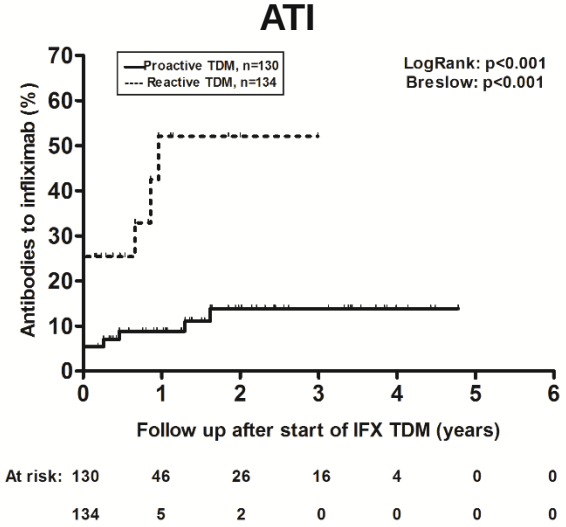
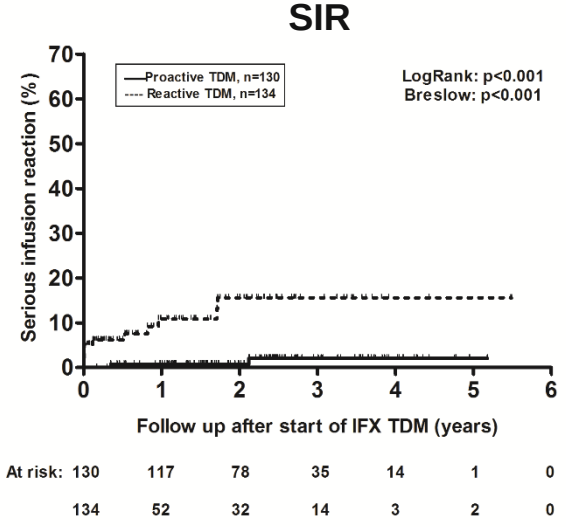
Papamichael et al. Clinical Gastroenterology and Hepatology 2017

Less IBD-Related Surgery, Hospitalization, ATI, and Serious Infusion Reactions with Proactive TDM









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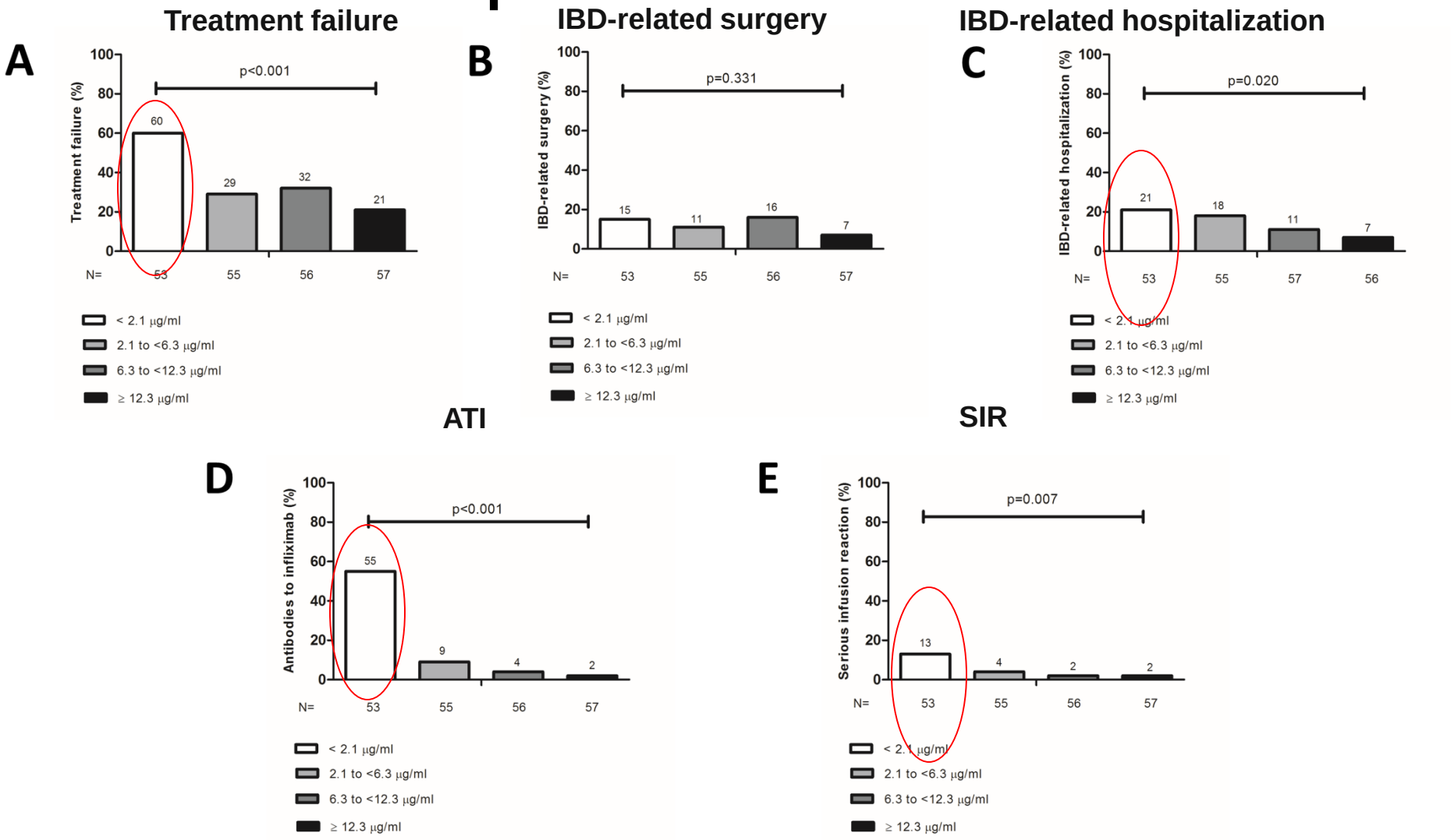
Papamichael K, et al. *Clin Gastroenterol Hepatol*. 2017;15(10):1580-1588.

Results: Infliximab TC quartiles associated with therapeutic outcomes of interest



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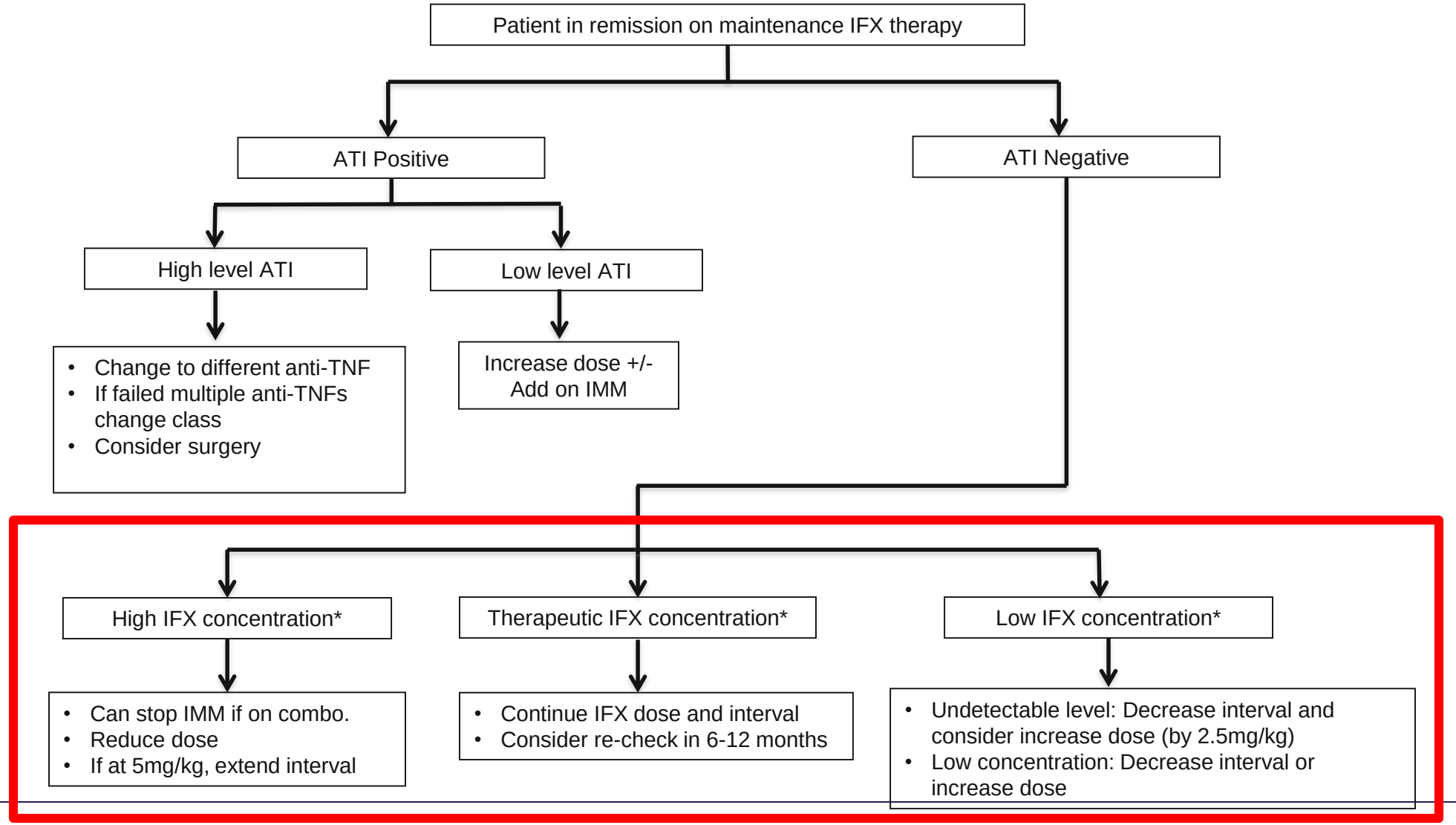
Papamichael et al. Clinical Gastroenterology and Hepatology 2017

Proactive testing algorithm: Dose optimize to infliximab trough > 5 (- 10ug/ml)



Standard dosing of infliximab is insufficient in the majority of pediatric CD

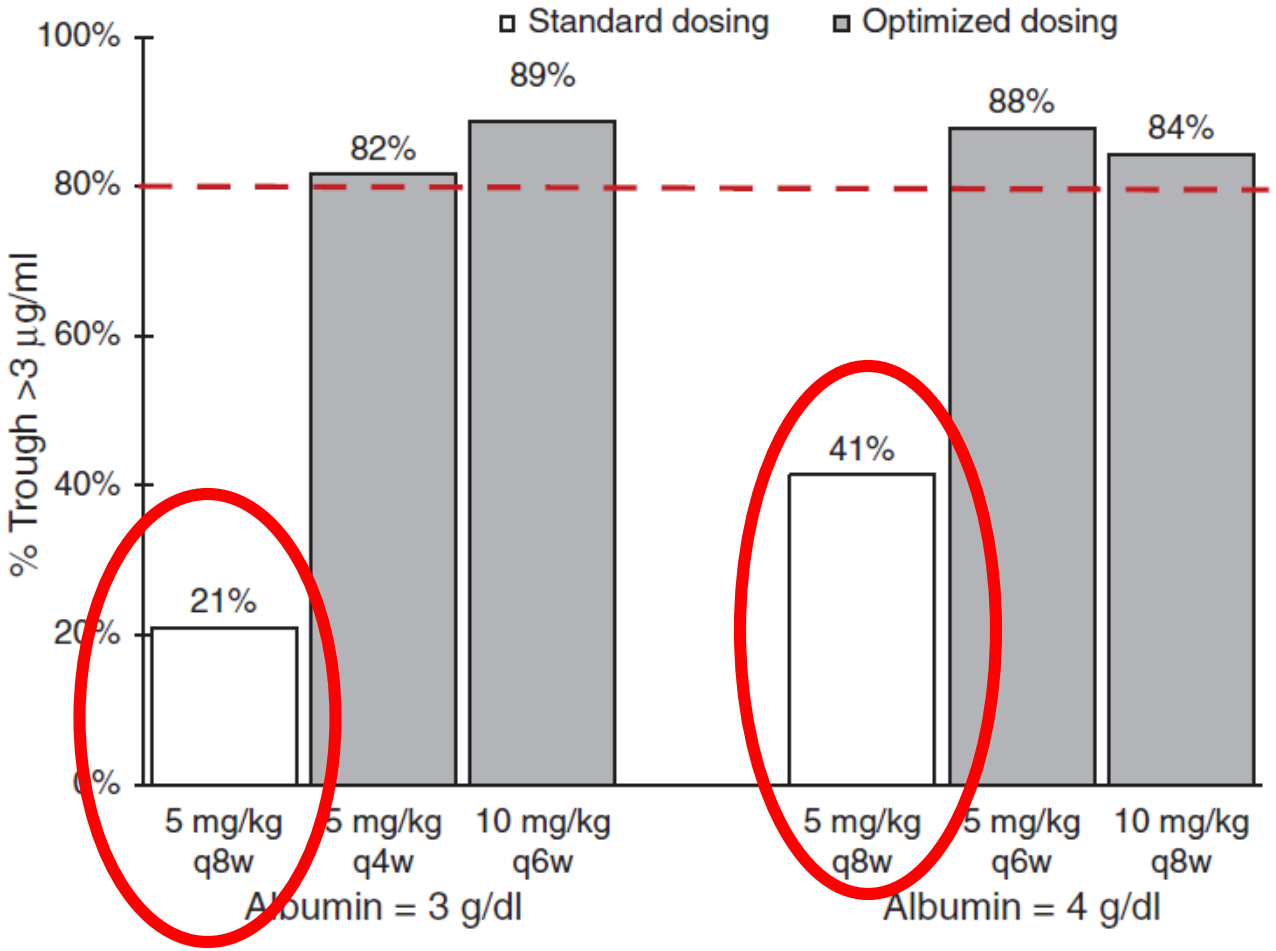
Monte Carlo model

REACH & ACCENT I

10 y.o. with CD

Wt., alb, IMM, ATI

Aim = trough > 3ug/ml



Frymoyer et al, JPGN 2016;62:723

What about proactive TDM following reactive testing?

- Aim: To evaluate long-term outcomes of proactive infliximab monitoring following reactive testing compared to reactive testing alone in patients with IBD in terms of treatment failure and IBD-related surgery and hospitalization.

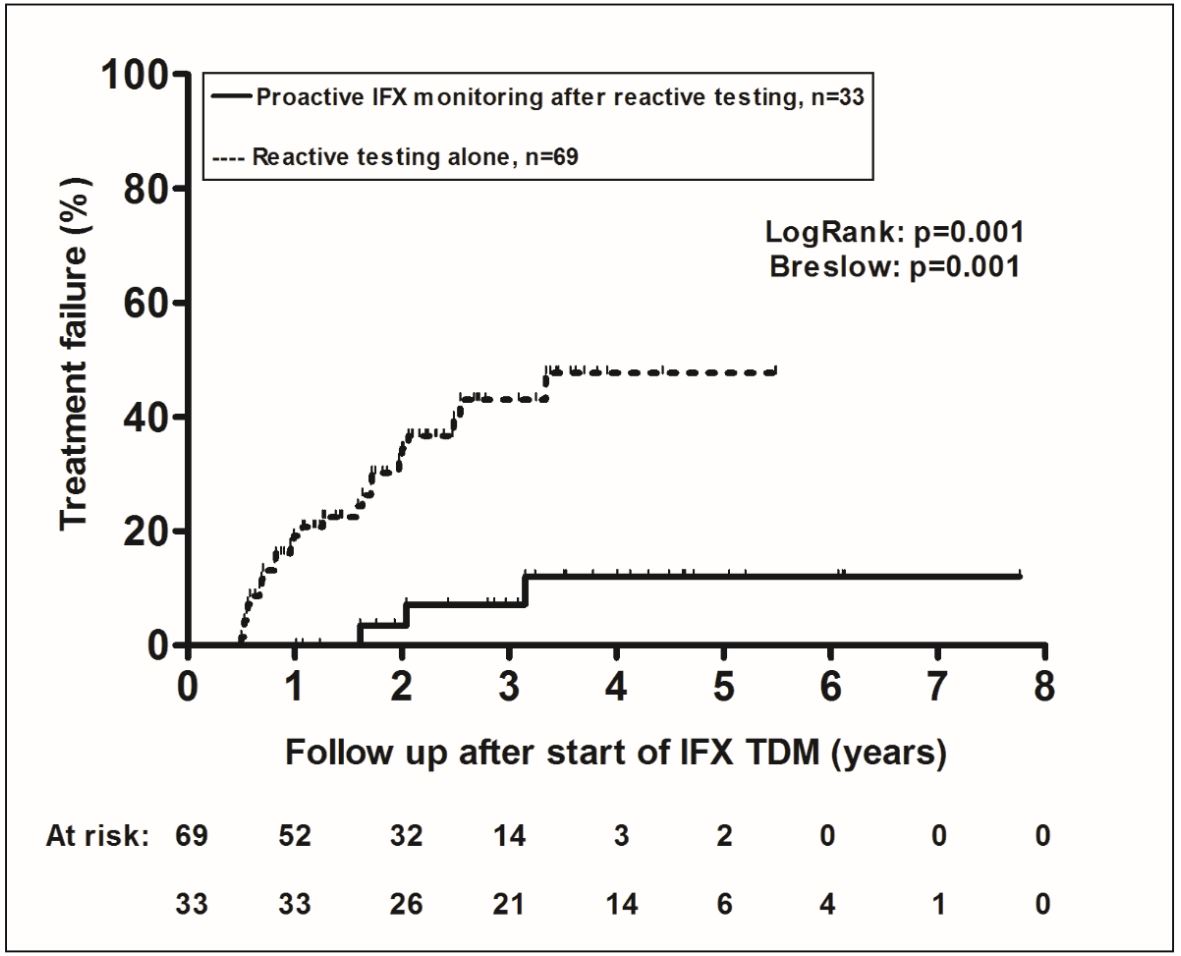
- Retrospective multi-center study.
- All consecutive IBD patients on infliximab maintenance therapy who underwent a first reactive testing from September 2006 to January 2015. Patients were followed through December 2015.
  - Group A: patients undergoing proactive infliximab monitoring after reactive testing performed for presumed loss of response or infusion reaction occurred
  - Group B consisted of patients undergoing reactive testing alone.
- Treatment failure was defined as infliximab discontinuation for loss of response or serious adverse event.

- 102 patients
- Median follow up of 2.7 (IQR 1.4-3.8) years
- No baseline differences between groups

Papamichael et al, JCC 2018 (accepted)

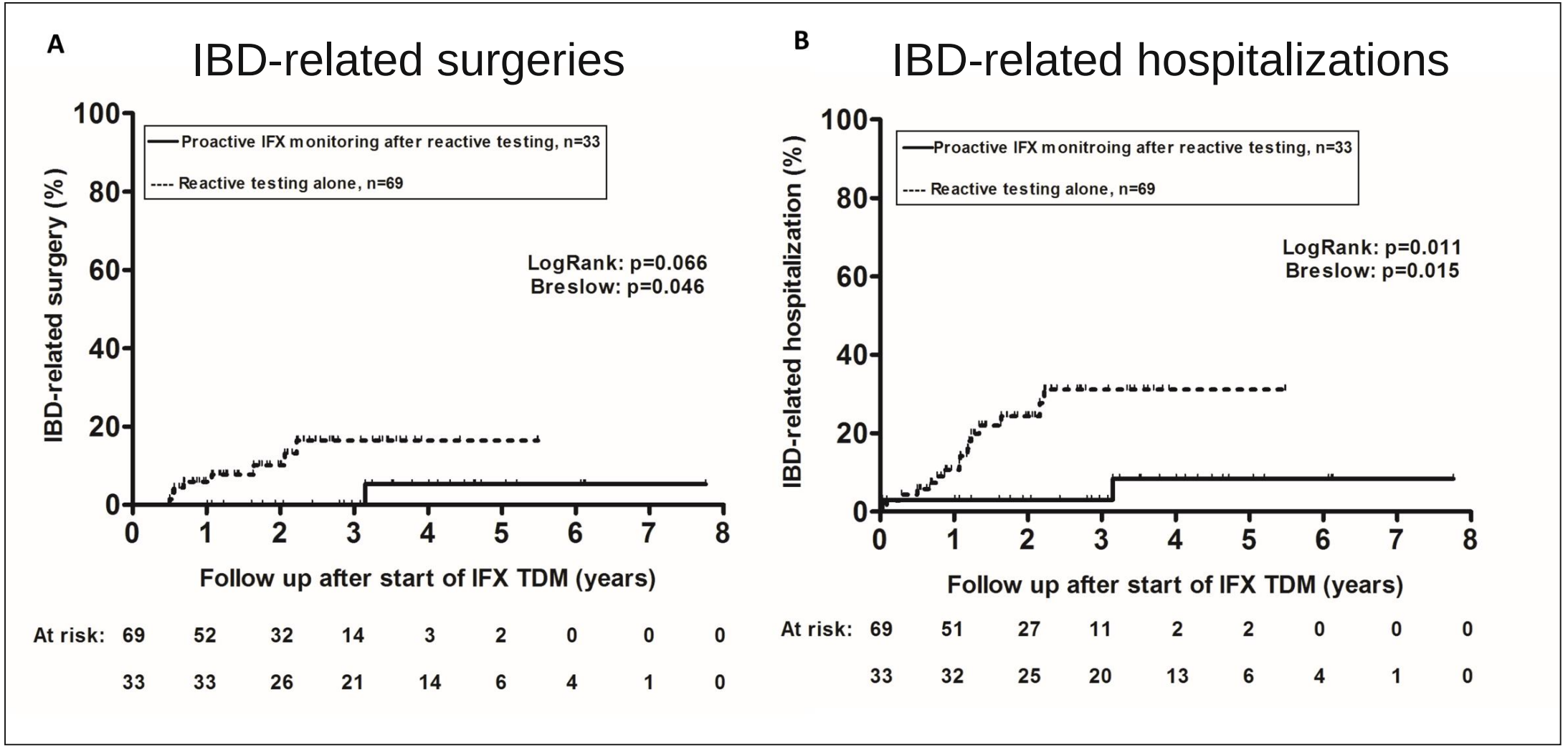
Table 1. Patient characteristics	Total cohort	Group A	Group B	P-value
N	102	33	69	
Male, (%)	54 (53)	16 (48)	38 (55)	0.672
Age at diagnosis, median (IQR), years	22 (18-31)	22 (18-31)	22 (18-32)	0.758
Age at infliximab initiation, median (IQR), years	33 (25-43)	37 (31-46)	30 (24-43)	0.072
IBD type: CD, (%)	70 (69)	24 (73)	46 (67)	0.562
UC extension: Pancolitis, (%)	16/30 (53)	4/9 (44)	12/21 (57)	0.694
CD behaviour: B1 / B2 / B3, (%)	36/70 (51) / 14/70 (20) / 20/70 (29)	11/24 (46) / 4/24 (16) / 9/24 (38)	25/46 (54) / 10/46 (22) / 11/46 (24)	0.486
CD location: L1 / L2 / L3 / L4, (%)	13/70 (19) / 23/70 (33) / 33/70 (47) / 3/70 (1)	5/24 (21) / 6/24 (25) / 12/24 (50) / 1/24 (4)	8/46 (17) / 17/46 (37) / 19/46 (41) / 2/46 (5)	0.787
Perianal fistulising disease, (%)	30/70 (43)	12/24 (50)	18/46 (39)	0.450
Smoking ever, (%)	21 (21)	8 (24)	13 (19)	0.603
Prior ileocolonic resection, (%)	16/70 (23)	7/24 (29)	9/46 (20)	0.383
IFX dosing other than 5 mg/kg q8w[a], (%)	46 (45)	14 (42)	32 (46)	0.832
Anti-TNF naive, (%)	95 (93)	30 (91)	65 (94)	0.679
Concomitant IMM[a], (%)	32 (31)	12 (36)	20 (29)	0.498
IFX concentration[a], median, (IQR), µg/ml	6.2 (1.5-11)	6.4 (2.4-11.1)	5.4 (1.4-11.1)	0.646
ATI[a], (%)	18 (18)	4 (12)	14 (20)	0.410
Type of assay[a]: HMSA, (%)	48 (47)	12 (36)	36 (52)	0.145

Less treatment failure in group that had proactive TDM following reactive testing as opposed to just reactive testing



Papamichael et al, JCC 2018 (accepted)

Less IBD-related hospitalizations in group that had proactive TDM following reactive testing as opposed to just reactive testing



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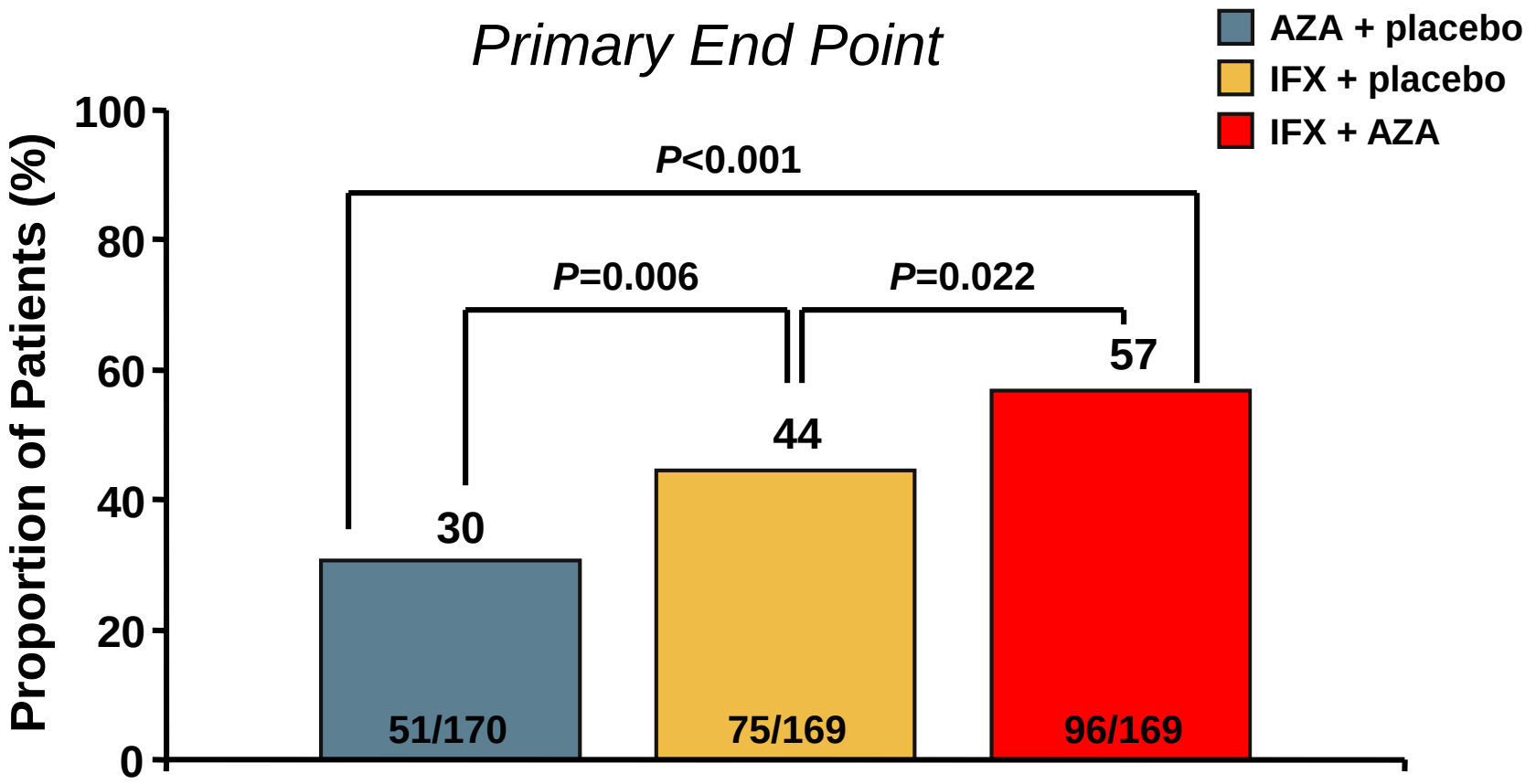
Papamichael et al, JCC 2018 (accepted)

Proactive TDM
(Optimized monotherapy with anti-TNF)

- Combination therapy with infliximab and immunomodulator improves outcomes

- Combination therapy with immunomodulator increases anti-TNF concentration and decreases anti-drug antibodies
- Combination therapy has been associated with increased adverse events (opportunistic infection, lymphoma and hepatosplenic T-cell lymphoma)
- Optimized monotherapy with anti-TNF may be an alternative to combination therapy

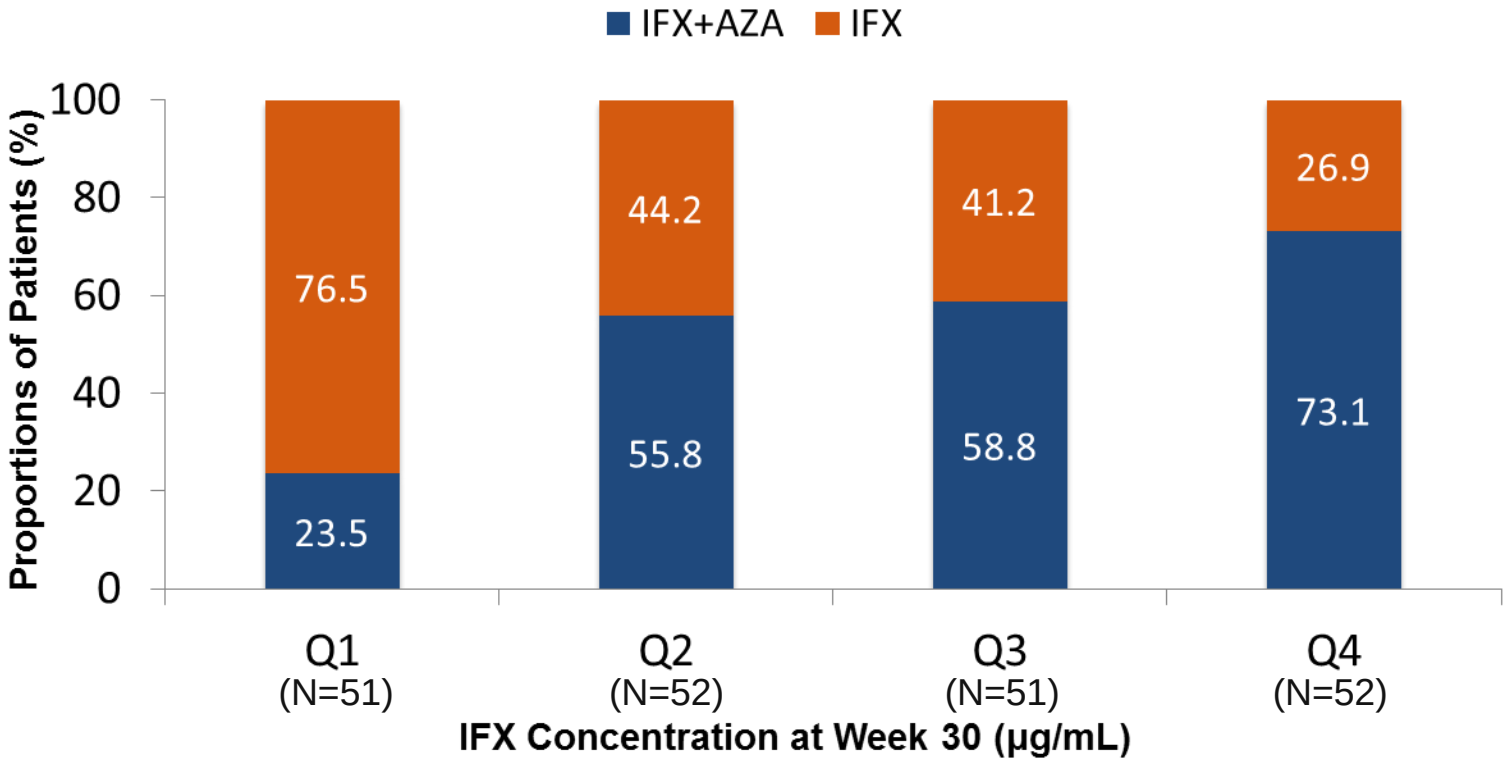
Best evidence for combination therapy is in biologic and immunosuppressive naïve patients with moderate to severe Crohn's (SONIC)



IFX, infliximab

Colombel JF, et al. *N Engl J Med*. 2010 Apr 15;362(15):1383-1395.

Patients in the IFX+AZA group contributed a greater number of patients to higher IFX concentration quartiles than IFX monotherapy

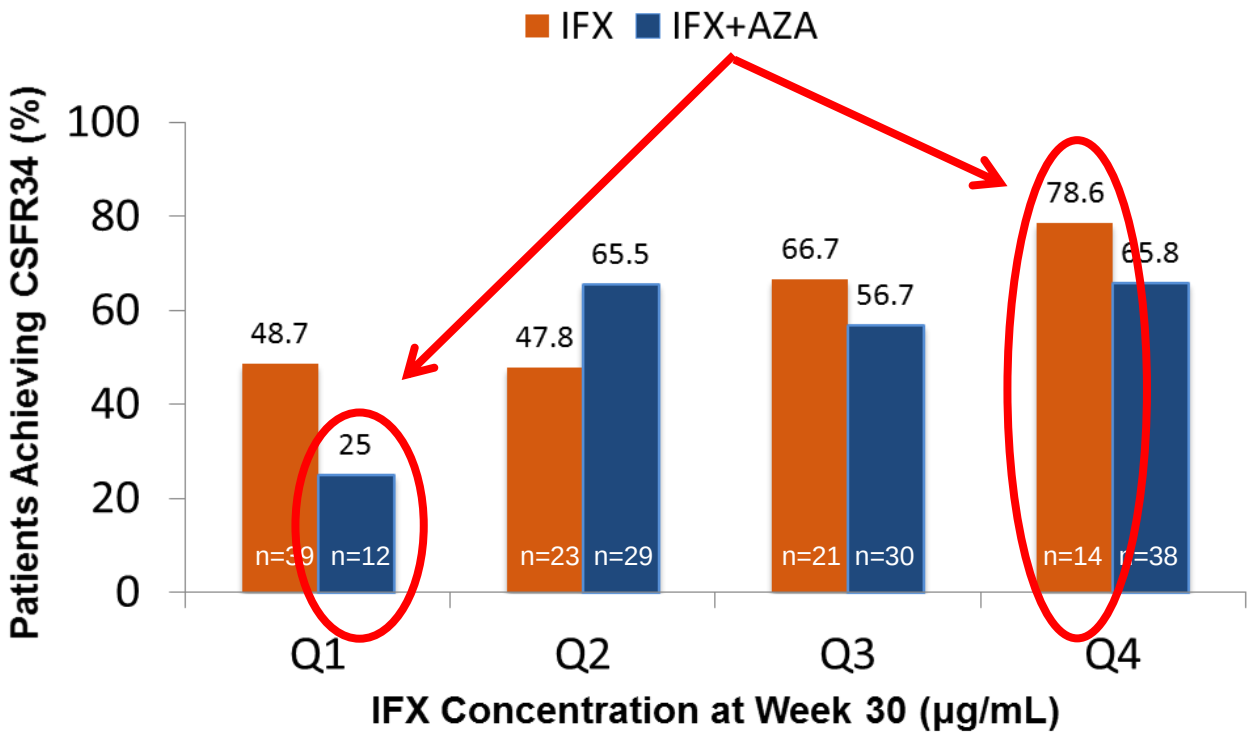


Q1: <0.84 µg/mL; Q2: 0.84 µg/mL to <2.36 µg/mL;
Q3: 2.36 µg/mL to <5.02 µg/mL; Q4: ≥5.02 µg/mL

Colombel JF, et al. Presented at ECCO 2017. Barcelona, Spain. Abstract P119.

Corticosteroid-Free Remission at Week 34 Depends on Serum Trough IFX Concentration (Week 30) Not Whether Patient is on Combination Therapy

- Within same quartile, comparable efficacy of monotherapy and combination therapy
- **More than twice as many patients achieved corticosteroid-free remission at week 34 from higher quartiles of IFX monotherapy compared to those on combination therapy with low IFX concentrations**



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Long term outcomes of "*optimized monotherapy*" with infliximab

- 31 patients
- All patients eventually titrated to IFX trough concentration > 3 ug/ml
- 83% of patients achieved a trough concentration > 5 ug/ml
- No patient stopped infliximab at end of data collection
- Median follow-up time: 3.4 years

- Continue to monitor trough concentrations

Vaughn B et al. Inflamm Bowel Dis 2014 Nov;20(11):1996-2003

Proactive TDM

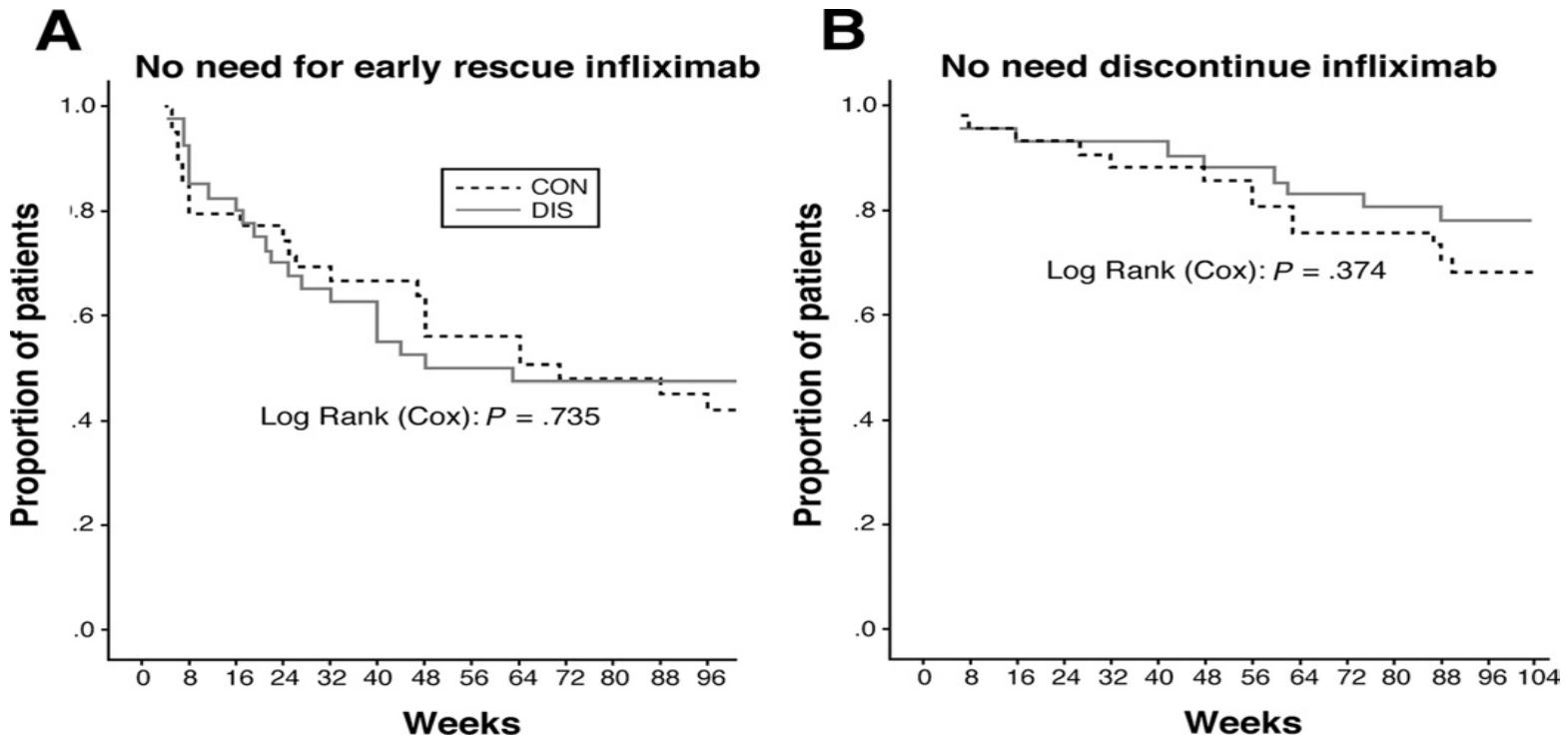
(When stopping immunomodulator (in combination with anti-TNF)

- Best data for combination therapy short-term (year)
- Stopping immunomodulator does not appear to affect 1-2-year remission rates
  - Associated with higher crp and lower anti-TNF concentrations
- Want adequate trough anti-TNF concentrations (before and) after stopping immunomodulator
  - Check anti-TNF concentrations before and after discontinuing immunomodulator

Van Assche et al. *Gastroenterology* 2008;134:1861–1868

Withdrawal of immunomodulator after 6 months of remission in combination with infliximab

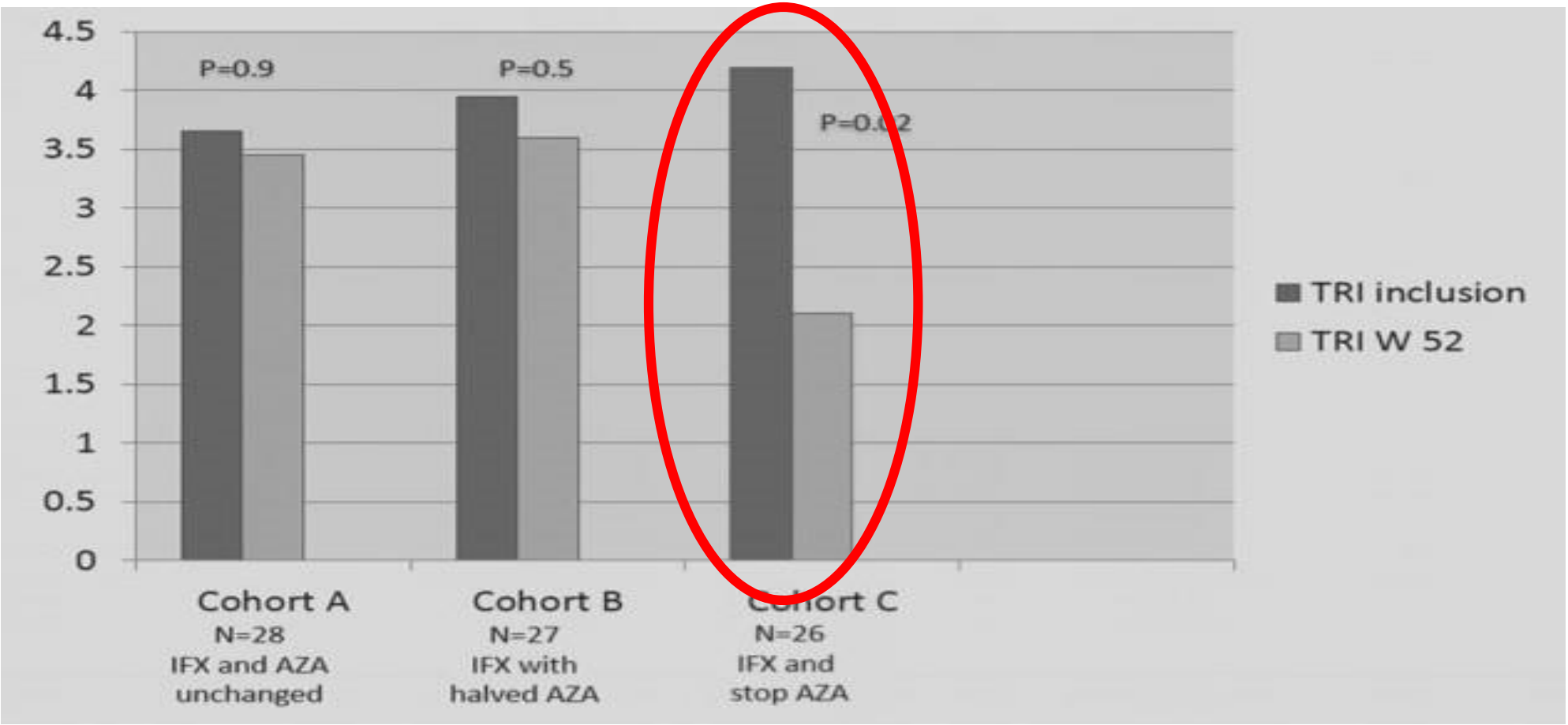
- Prospective RCT
  - 40 DIScontinued IMM
  - 40 CONtinued IMM
  - Followed for 2 years



Immunomodulator withdrawal is
associated with significantly lower infliximab trough and higher CRP

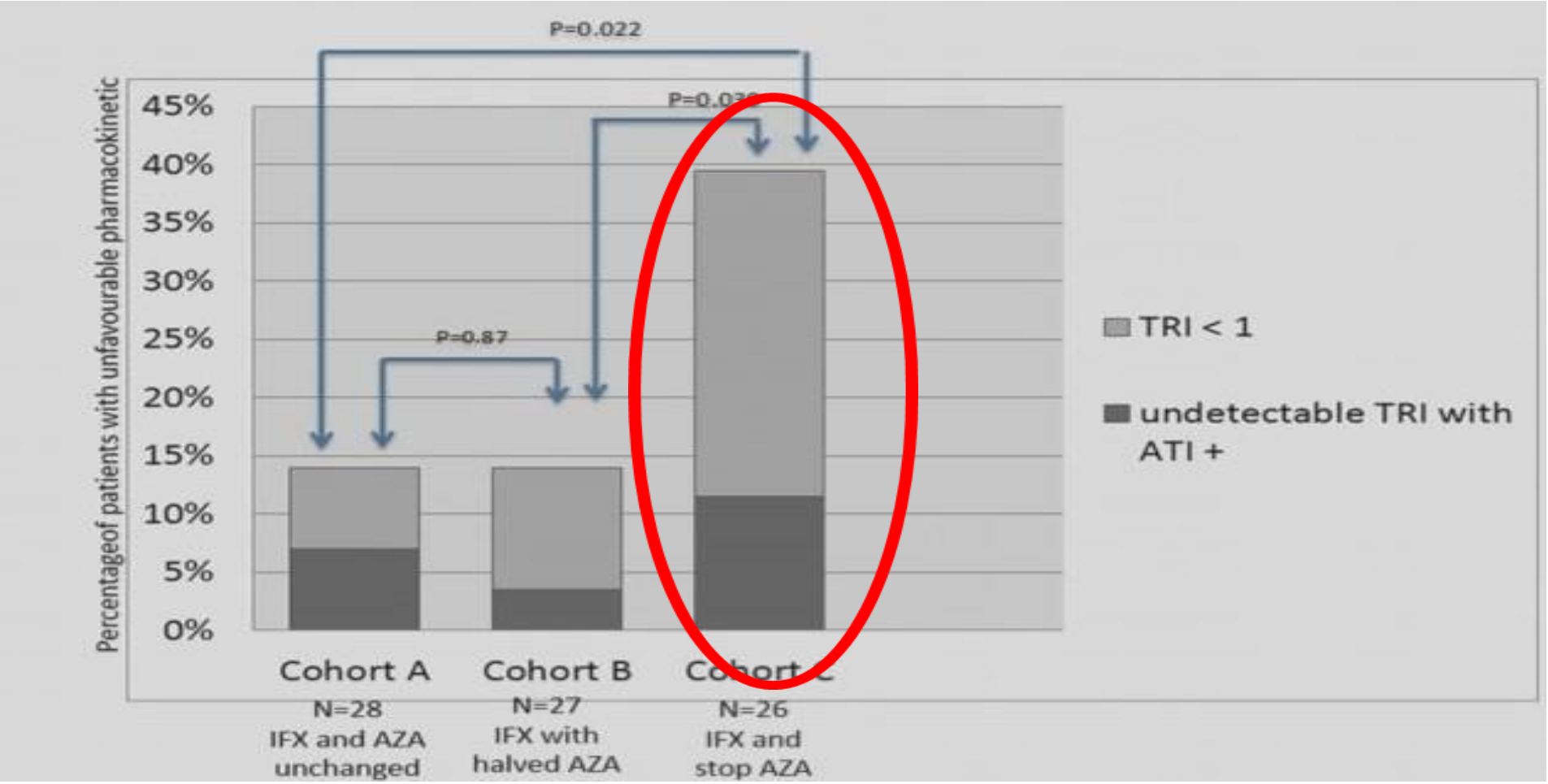
Van Assche et al. *Gastroenterology* 2008;134:1861–1868

Infliximab concentrations halved with stopping azathioprine



Tedesco et al, DDW 2016

Number of patients with infliximab trough < 1 went up to 40% with stopping AZA



Tedesco et al, DDW 2016

Proactive TDM
(Induction)

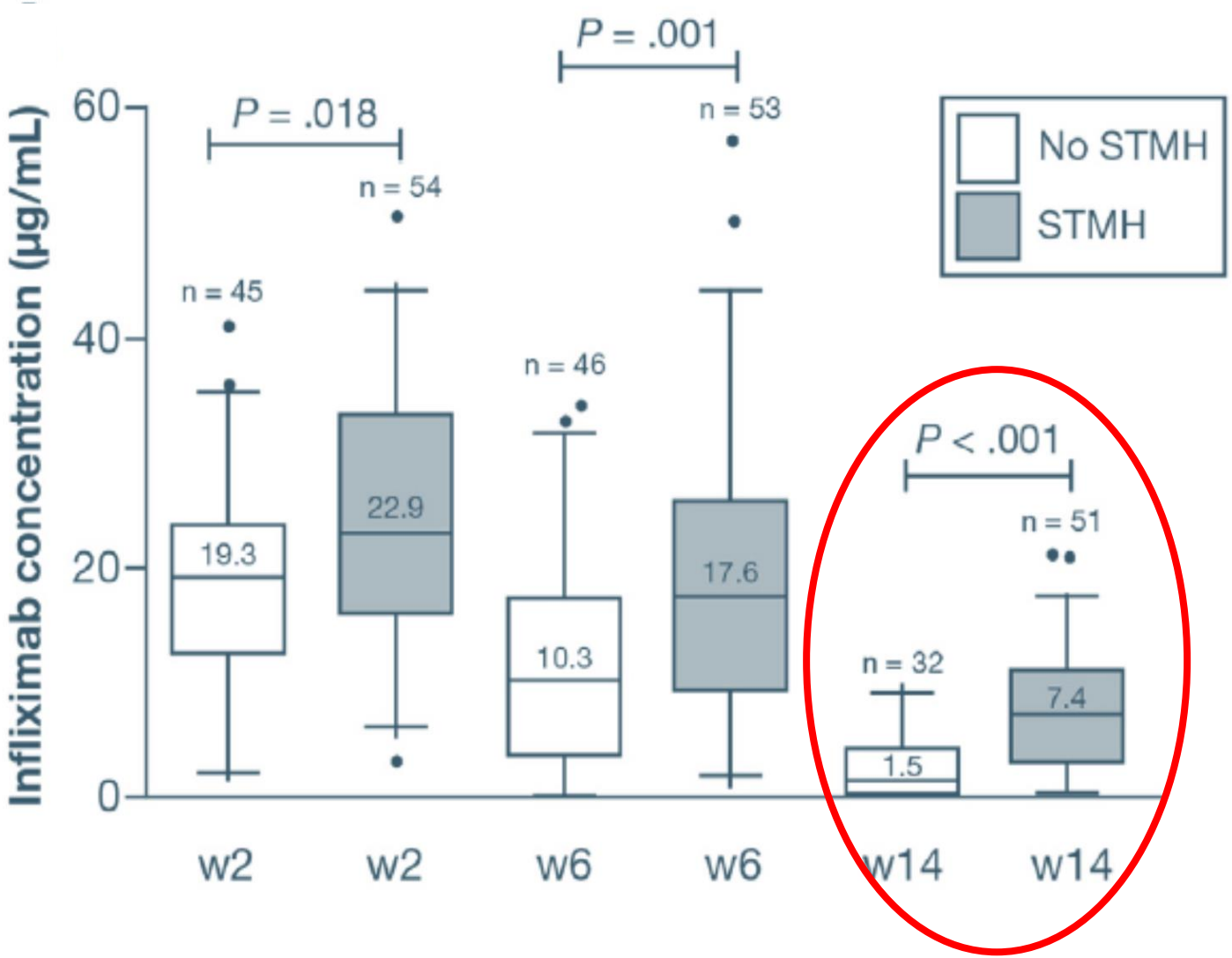
- Patients with active disease require more drug
- Early drug concentrations correlate with short-term and long-term outcomes

Moderate-severe UC: ATI develop early and are associated with low infliximab concentrations and worse outcomes

- 19 patients with mod-severe UC treated with infliximab
- 58% endoscopic response (week 8)
- **Infliximab concentrations at week 6 higher in responders**
  - 8.1ug/mL vs. 2.9ug/mL in non-responders (p=0.03)
- **6/8 non-responders had +ATI** (vs. 1/11 responders) (p<0.01)
  - **ATI seen as early as day 18**
- Patients with high CRP had lower infliximab concentrations (p=0.001)

Brandse et al, Clin Gastroenterol Hepatology 2016

Early infliximab trough concentrations correlate with short term mucosal healing in UC



Papamicheal K et al. Clinc Gastroenterol Hepatol 2016 Apr;14:543-9

Early IFX trough concentrations are associated with persistent remission in pediatric IBD patients

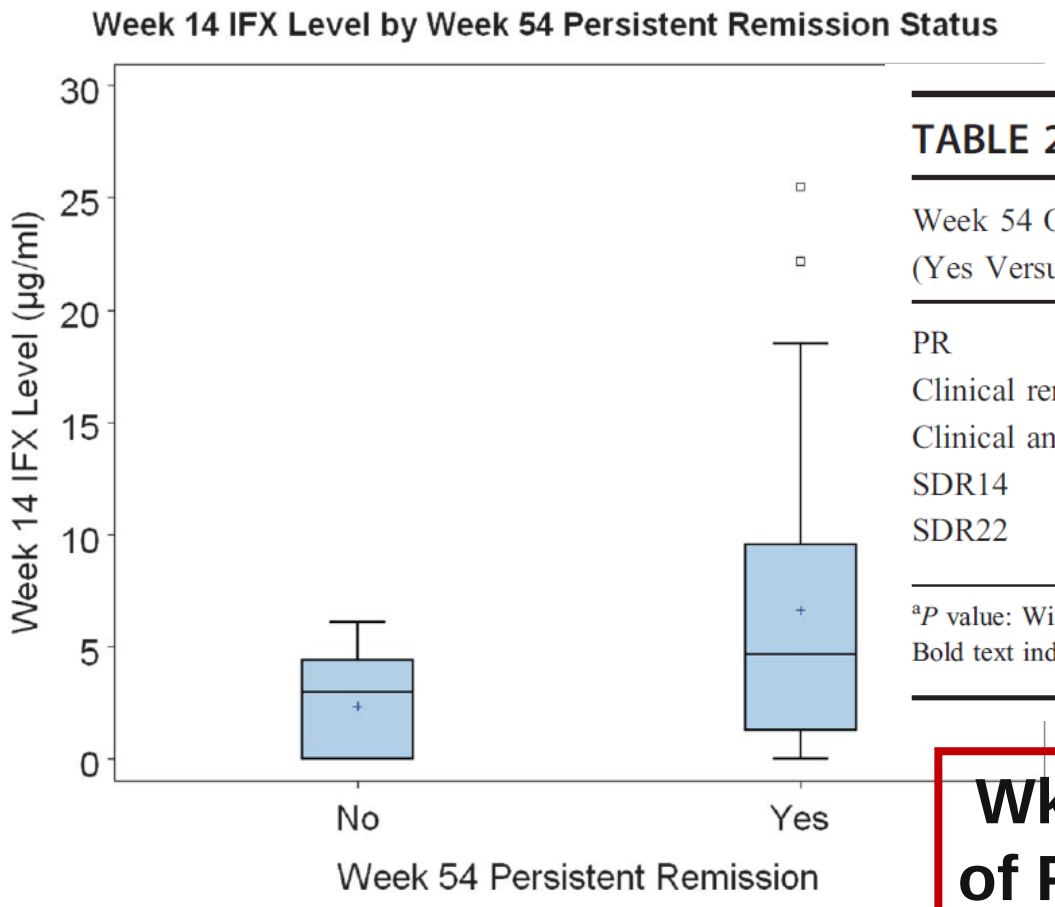


TABLE 2. Week 14 Infliximab Levels and Outcomes

Week 54 Outcome (Yes Versus No)	IFX14 Median Level, µg/mL	P^a
PR	**4.7 versus 2.6**	**0.03**
Clinical remission	3.2 versus 2.2	0.07
Clinical and laboratory remission	4.2 versus 3.0	0.07
SDR14	**5.5 versus 3.1**	**0.05**
SDR22	**5.1 versus 3.0**	**0.04**

[a]*P* value: Wilcoxon rank sum test.
Bold text indicates significant *P* values.

Wk 14 IFX > 7 = PPV 100% of Persistent Remission

Singh (Dubinsky) Inflamm Bowel Dis 2014

Issues with drug concentration monitoring

- Optimal trough concentration window is unclear
- Timing of testing
- Test that is accurate, accessible, and inexpensive

- Prospective data on implementation of TDM

AGA TDM Guidelines: Reactive concentrations

Table 4. Suggested Target Trough Concentrations When Applying Reactive Therapeutic Drug Monitoring in Patients With Active Inflammatory Bowel Disease on Maintenance Therapy With Anti–Tumor Necrosis Factors[a]

Drug	Suggested trough concentration, μg/mL	Comments[b]
Infliximab	≥5	Six studies (929 patients) provided data on proportion of patients not in remission above predefined infliximab thresholds (1, 3, 5, 7, and 10 μg/mL). Based on these, proportion of patients not in remission decreased from 25% when using an infliximab threshold of ≥1 μg/mL, to 15% with an infliximab trough concentration of ≥3 μg/mL, to approximately 4% with an infliximab trough concentration of ≥7 μg/mL or ≥10 μg/mL
Adalimumab	≥7.5	Four studies provided data on proportion of patients not in remission above adalimumab trough concentration >5.0 ± 1 μg/mL or 7.5 ± 1 μg/mL. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 17% when using an adalimumab threshold ≥5.0 ± 1 μg/mL, to 10% with an adalimumab trough concentration of ≥7.5 ± 1 μg/mL. Different studies used different assays, and there are limited data on comparability of trough concentrations identified in different assays for adalimumab It is unclear what proportion of patients on standard (40 mg every other wk) or escalated adalimumab dosing (40 mg every wk) would be able to achieve these thresholds
Certolizumab Pegol	≥20	One study provided data from an exposure response pooled analysis from 9 trials. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 42% when using a certerolizumab threshold of ≥10 μg/mL to 26% with a certolizumab trough concentration of ≥20 μg/mL
Golimumab	Unknown	There is a lack of sufficient evidence available to establish a target trough goal

[a]Studies used to derive different target trough concentrations were cross-sectional studies of patients on maintenance therapy in various stages of remission/response, to identify what proportion of patients were in remission (or not in remission), above and below specific thresholds. They were not specifically designed to evaluate patients who had a secondary loss of response.
[b]Details are available in accompanying Technical Review.

Feuerstein et al, Gastroenterology 2017

Consensus statement on TDM in IBD by Australian IBD Consensus working group

Statement	Acceptance (%)	EL	RG
Target drug trough levels			
17. In IBD patients with luminal disease a steady state trough infliximab level between 3 and 8 µg/mL is generally recommended	96	II	B
18. In IBD patients with luminal disease a steady state adalimumab trough level between 5 and 12 µg/mL is generally recommended	95	II	C
19. In certain situations higher or lower trough levels than the above ranges may be appropriate	100	III3	B

Mitrev et al, APT 2017

Optimal drug concentrations (µg/mL) ?

	Outcome	Conc. (µg/mL)	What I do (remission)	Reactive (AGA)	What I do (reactive)
Infliximab	Clinical remission	>5	>5	**> 5**	**>10-15**
	Deeper remission	>8	**>10**		
	Week 14	>7	>10		
Adalimumb	Clinical remission	>5	>5	**> 7.5**	**>10-15**
	Deeper remission	>8	**>10-12**		
	Week 4	>7	>10		

Ustekinumab > 4.5 µg/ml
Vedolizumab > 27.5 (week 6)
Certolizumab > 23.3 (week 8)

Battat et al, CGH 2017
Williet et al. 2016
Colombel et al. 2014
Feuerstein et al, 2017

Attitudes and barriers towards therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease

Primary Aim:

- Determine the proportion of physicians performing TDM of anti-TNF therapy in patients with IBD
- Determine barriers towards the implementation of TDM

Methods:

- Web-based questionnaire distributed to:
- American College Gastroenterology (ACG) and Crohn's Colitis Foundation of America (CCFA)

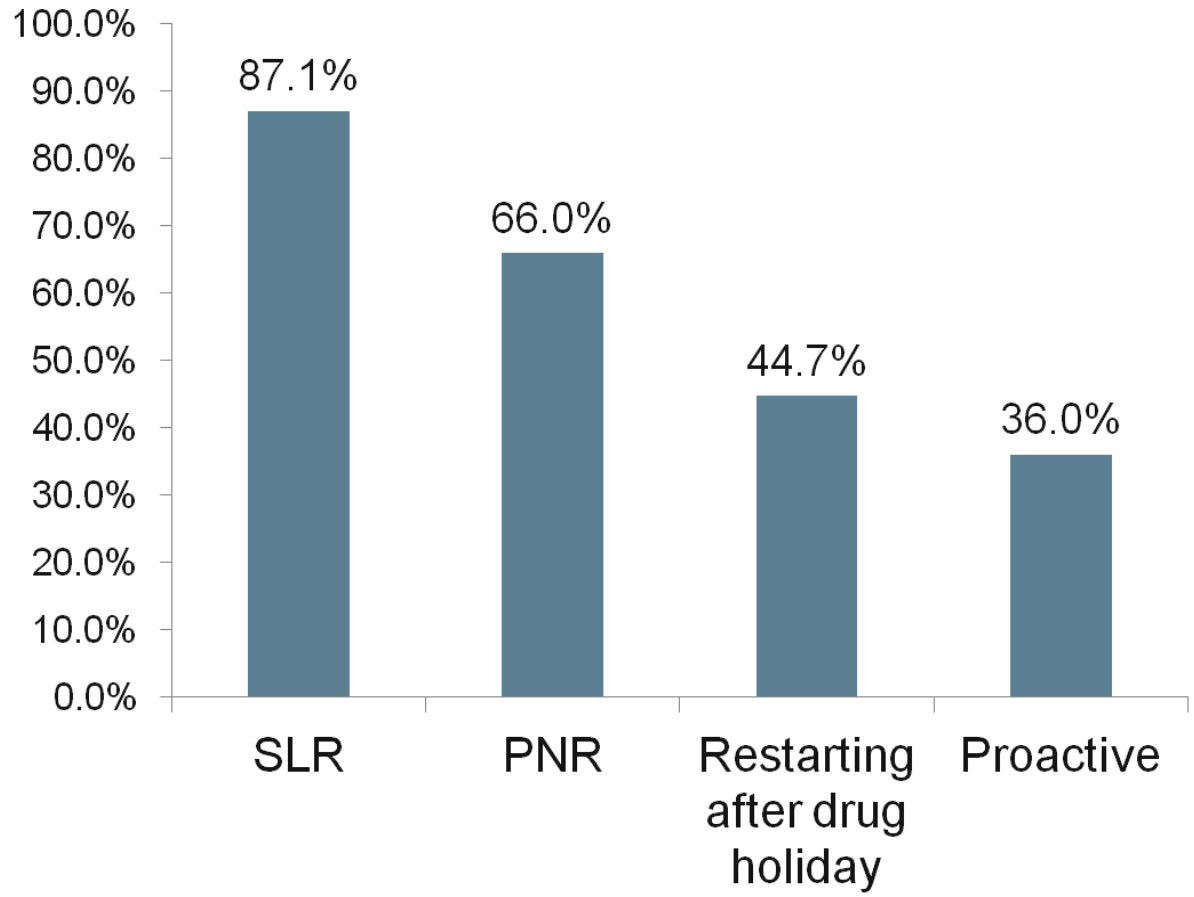
403 respondents

Grossberg et al, IBD 2017

Results: Use of TDM

Q: Do you check anti-TNF drug concentrations and anti-drug antibodies?

90.1% of gastroenterologists surveyed answered **YES**



Grossberg et al, IBD 2017

Barriers to TDM

Top 3 most important barriers to TDM	N, (%)
Uncertainty about insurance coverage of test	314 (77.9)
High out-of-pocket cost for the patient	308 (76.4)
Time lag from serum sample to result of TDM	155 (38.5)
Lack of good evidence-based medicine of the usefulness of TDM in IBD	144 (35.7)
Lack of availability of TDM in clinical practice	84 (20.8)
Lack of knowledge of how to interpret and what to do with the results of TDM	80 (19.9)
TDM is cumbersome and/or time consuming	52 (12.9)
Lack of overall knowledge of TDM	39 (9.7)

If all barriers were removed:

Physicians already using TDM would do it more proactively

36% -> 68%

81.6% of gastroenterologists who do not currently use TDM, would use TDM if all barriers were removed.

Grossberg et al, IBD 2017

Common US Labs for TDM

Laboratory	Drugs	Assay	Drug Tolerant	Comments
Prometheus	IFX, ADA, VDZ	HMSA	Yes	•Best studied •$$$ - can be significant out of pocket costs
LabCorp/ Esoterix	IFX, ADA, VDZ, GOL	ECLIA	Yes	•Better coverage •Antibody levels can be quite confusing (ng/ml).
Mayo	IFX	?	No	•Better coverage •Doesn't measure antibody with drug present
Miraca	IFX, ADA, CTP, VDZ, UST, GOL	ELISA	No	•Most tests available •Better coverage •Can't measure antibody with drug present

In practice

- Know your test (and use it)
  - Drug tolerant assay?
  - Cost (to patient)?
- Know what to do with your results
  - BRIDGe; Australian Consensus Statement
- If nothing else, test reactively
- Proactive testing likely best
  - Check after induction
  - Follow during maintenance

What to do with the results?

Anti-TNF optimizer

Found at: www.BRIDGeIBD.com

Accessible on all devices (smart phones, tablets and computers)

Melmed et al, CGH 2016

TDM conclusions (so far)

- Positive association between trough concentration and clinical outcomes
- Drug concentrations and anti-drug antibodies help guide decisions
- Reactive TDM
  - More cost effective and more appropriately directs therapy than empiric dose escalation
  - Proactive following reactive is better than reactive testing alone
- Proactive TDM (maintenance)
  - Improves outcomes and it is cost-effective
  - When compared with reactive TDM, decreases risk of treatment failure, IBD-related surgery and hospitalization, ATI, and SIR.
  - Optimized monotherapy may be alternative to combination therapy
  - If you stop concomitant immunomodulator, check anti-TNF concentration prior to and after discontinuation
- Proactive TDM (induction)
  - Early drug concentration correlates with longer-term outcomes
- Issues – optimal trough concentration window; timing of testing; test that is accurate, accessible, and inexpensive; prospective data on implementation of TDM

Question

Which has been associated with a decrease in monoclonal antibody drug clearance?

A. High baseline CRP
B. Low albumin
C. Concomitant use of immunomodulator
D. Presence of anti-drug antibodies

Question

- Proactive TDM when compared to reactive TDM was shown to be associated with:
- A. Fewer IBD-related hospitalizations
- B. Less antibody to infliximab formation
- C. Less treatment failure
- D. All of the above