nationwide RCT of stopping TNFi in stable LDAS RA: POET study

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DREAM platform		P van Riel & M vd Laar
Steering committee	A*dam	W Lems; DJ Schaardenburg
	R*dam	M Hazes
	Leiden	R Allaart
	Utrecht	J Tekstra
	Maastricht	A Boonen
	Nijmegen	P van Riel / I Meek/A den Broeder
	Enschede/Zwolle	M vd Laar/ M Hoekstra
	Groningen/Leeuwarden	A Brouwers/ R Bos
NVR Board	B Dijkman/GA van Albada/ H Bernelot-Moens/ R Landewe	
Patients' Society		G Willemsen

Nederlandse Vereniging voor Reumatologie

VieCuri Medisch Centrum voor Noord-Limburg

Radboudumc

disclosures

Tim L Jansen

Grant	ministry of health/ZonMW (POET)
	Abbvie (POET-US)(endothelial POET)
	UCB (open label POET 2nd yr)
	ACR/EULAR (SugaR: update gout criteria)
Lecture fee	Ardea/AstraZeneca; Aspen; BMS; Menarini
Advisory board	Abbvie; Actelion; BMS; Janssen; Pfizer; Roche; UCB
	Ardea/AstraZeneca; Menarini; Novartis

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Rheumatoid arthritis

Chronic synovitis
Periferal joints
Erosive & destructive

Inflammatory Pain
Loss of Quality of Life
- Fatigue
Loss of working capabilities
Cardiovascular mortality

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IQ HealthCare
Radboudumc

Start csDMARD early
MTX
MTX/HCQ/GC

TightControl
T2T

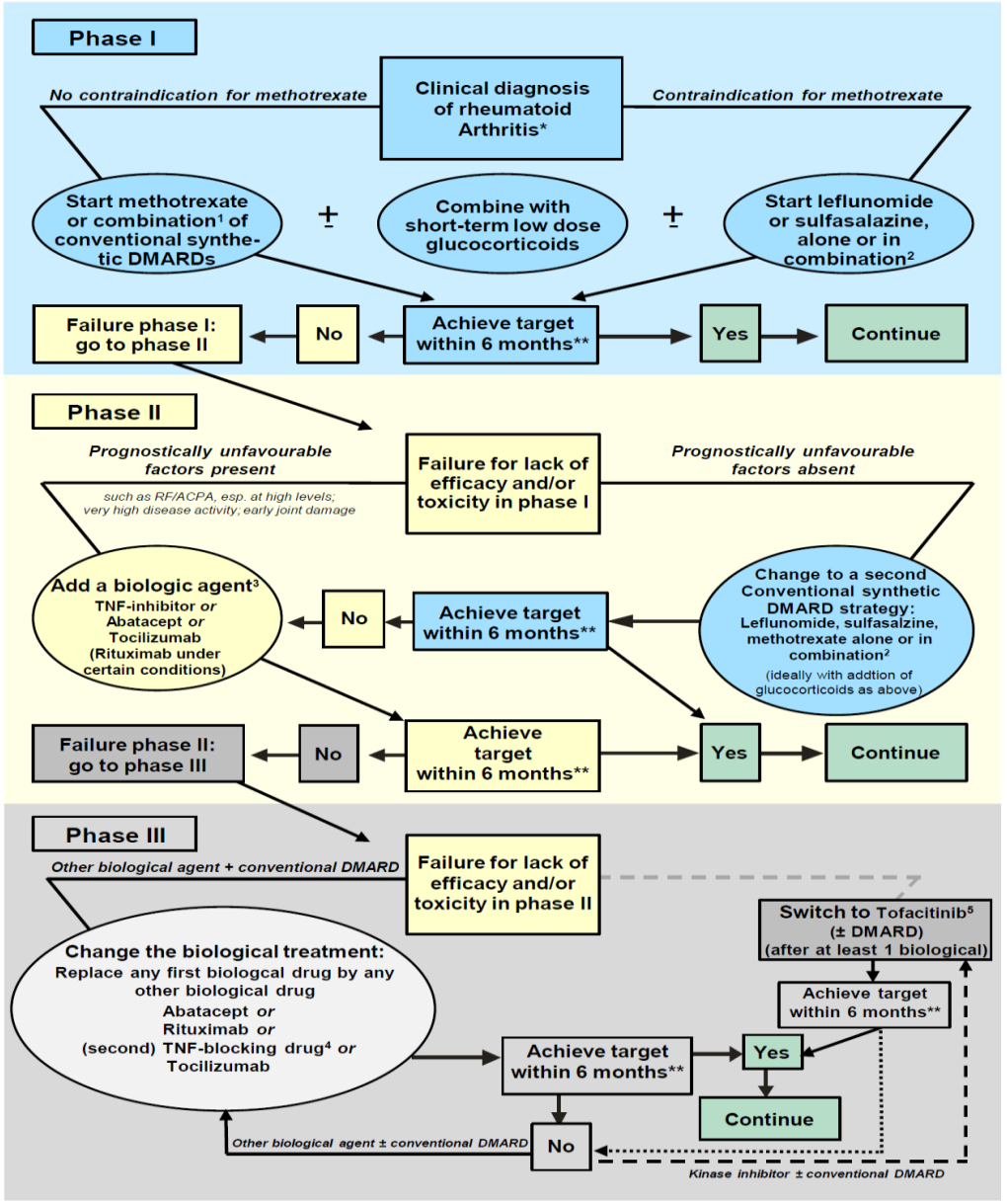
add bDMARD:
TNFi/ABCT/TCZ
RTX

change biologic

2yrs: CR

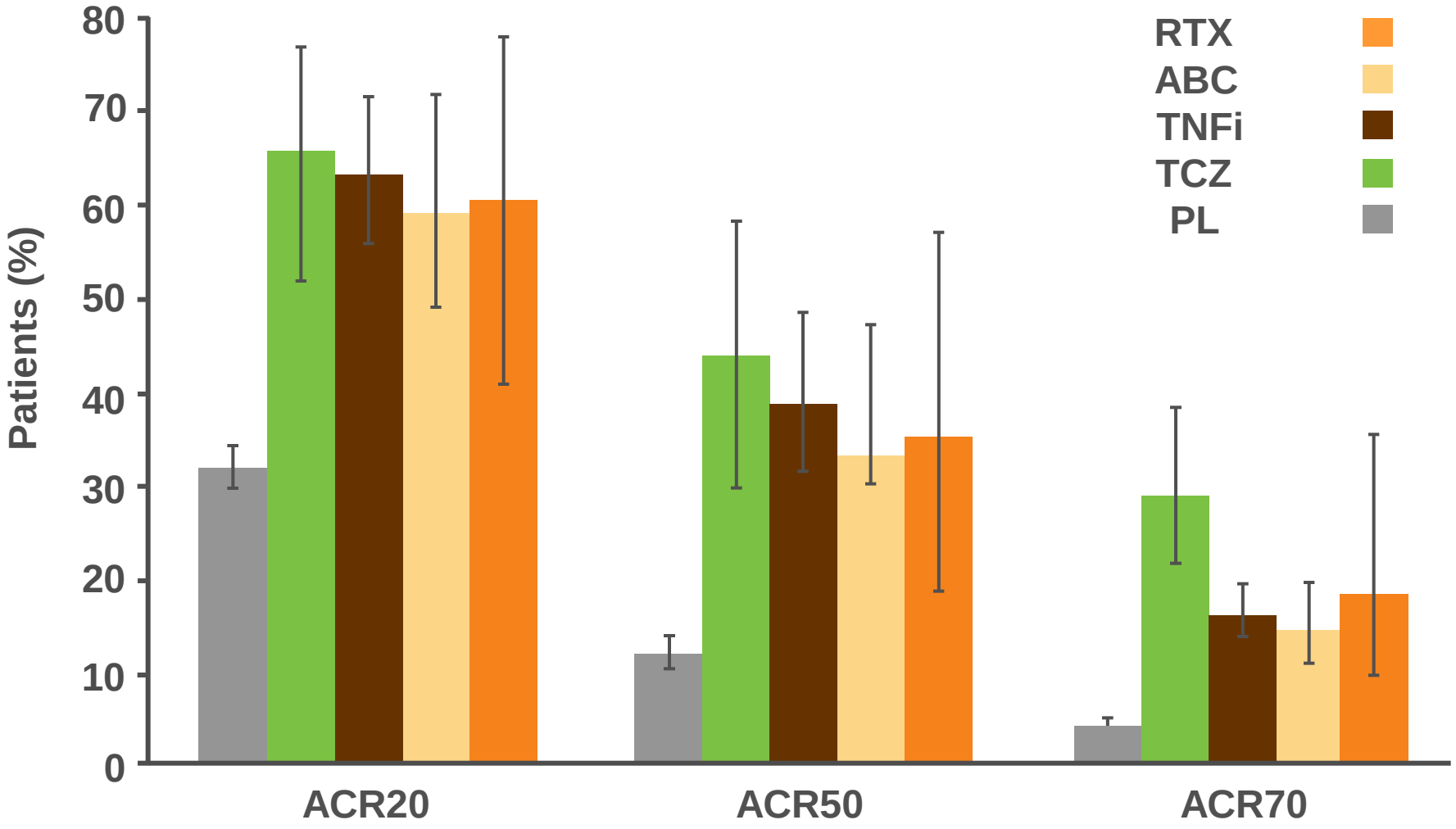
taper/stop?

Figure 1. Algorithm based on the 2013 EULAR recommendations on RA management



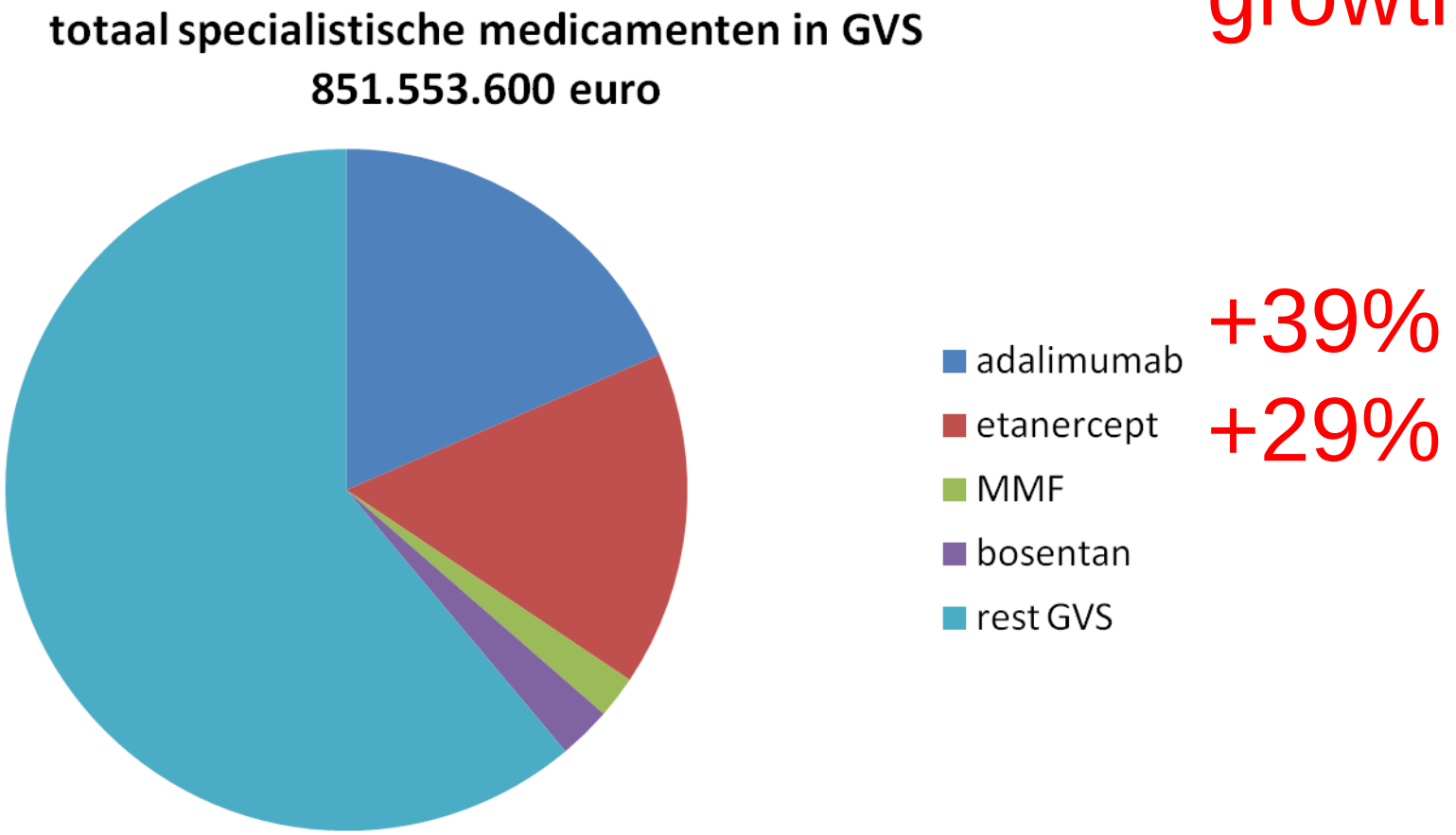
*2010 ACR-EULAR classification criteria can support early diagnosis; **The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed, if no improvement is seen after 3 months. [1]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine; [2]Combinations of sulfasalazine or leflunomide except with methotrexate have not been well studied, but may include combining these two and also with antimalarials; [3]these circumstances are detailed in the text; [4]Adalimumab, certolizumab, etanercept, golimumab, infliximab or respective well studied and FDA/EMA approved biosimilars; [5]where licensed.
Lines: Full black line, recommended; as shown; grey interrupted line: recommended for use after biologics failure (ideally two failed biologics); interrupted black line: recommended after two biologics failed, but efficacy and safety after failure of abatacept, rituximab and tocilizumab not sufficiently studied; black dotted line: possibly recommended, but efficacy and safety of biological use after tofacitinib failure unknown at the time of developing the 2013 update of the recommendations.

response: biologics vs conventional synthetic DMARD: highly effective therapy



Netherlands in 2009

annual growth

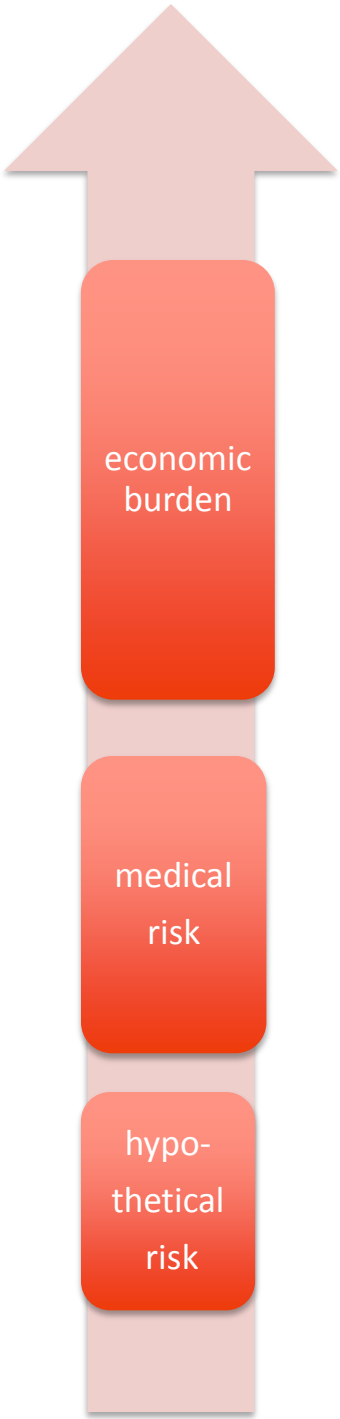


Targets in RA treatment

revolutionized in 2 decades

1	2	3
PAINLESS	**CARE**	**CURE**
pyramid	Early csDMARD	Strategy: BEsT T2T+ TC Early TNFi combi Early Bcell depletion
NSAID GC Au/ d-pen/ azathioprine Later SSZ/MTX	MTX GC-MTX: COBRA-lookalikes Biologic tapering (DRESS)	DFR (Ten Wolde) **BFR** (POET)

POET – 12 mos



Reasons to TNFi stop

- overtreatment = high expenses
  - suboptimal cost-effectiveness:
    - » Expensive if needed, but Cheap if adequate
    - » Maintenance phase ≠ Remission Induction phase
- infection risk
  - banal: first half year after start
  - low virulent mo / TBC : ongoing risk during TNFi therapy
- cancer risk
  - NMSC (sunny regions of world)
  - other > 15 yr?
- antibody formation / cross reactivity

TNFi riskminimisation

Opportunistic infections and TBC

Allergic reactions / anafylaxis

Lymphoma / other malignancy

Congestive heartfailure

Pancytopenia: L / T cytopenia

Demyelinisating disease / MS

Vaccination programme

Sarcoid-like granulomas

Leucemia

Lupus-like syndrome

Hepatobiliary disease

POET – TNFi$_{STOP}$

March 2015 = 12 months

The POET study

Funded by ZonMW/Dutch Ministry of Health

Demands:
-rheumatologists in the lead
-alternative for 30-40% annual increase in cost
of TNFi in NL: -dose reduction
-stop
-multicentre study with nationwide robust data
-commitment:
centres from non-DREAM +
centres from DREAM

POET – TNFi$_{STOP}$

March 2015 = 12 months

The POET study

Primary aim:
-Is it feasible in LDAS RA to safely stop TNFi and to restart if needed

Primary Outcome:
- Flare Risk
- Relative Flare Risk in stop vs cont arm

POET – TNFi$_{STOP}$

12 months

The POET study

Secondary Outcome:
In stop vs cont arm
-Use of TNFi after 12 mos
-Medical cost/effectiveness
-DAS28 and complete remission percentage at T= 3-6-9-12 mos
-Flare predictors
-Patient-reported outcome measures (PROMs)

In stop group:
-Safety&effectiveness at reinstitution of TNFi
-Time to flare and/or reinstitution of TNFi
-Experienced quality of care by subjects

POET – TNFi$_{STOP}$

12 months

Potential Optimalisation Expediency TNFi:

-Multicenter Open Label RCT (2:1 block randomisation) in

-LDAS RA (<3.2) on stable csDMARD + TNFi

-Inclusion criteria:

- -RA according ACR 1987 criteria
- - >1 yr treated with csDMARD + TNFi: stable dose
- -Stable low disease activity: DAS28<3.2 at 2 visits
- -If no DAS28 available:
  - -LDAS at discretion rheumatologist, AND
  - -Proof of CRP<10 during at least 6 mos

POET – TNFi$_{STOP}$

12 months in all 817

Potential Optimalisation Expediency TNFi:

-Multicenter Open Label RCT (2:1 block randomisation) in

-LDAS RA (<3.2) on stable csDMARD + TNFi

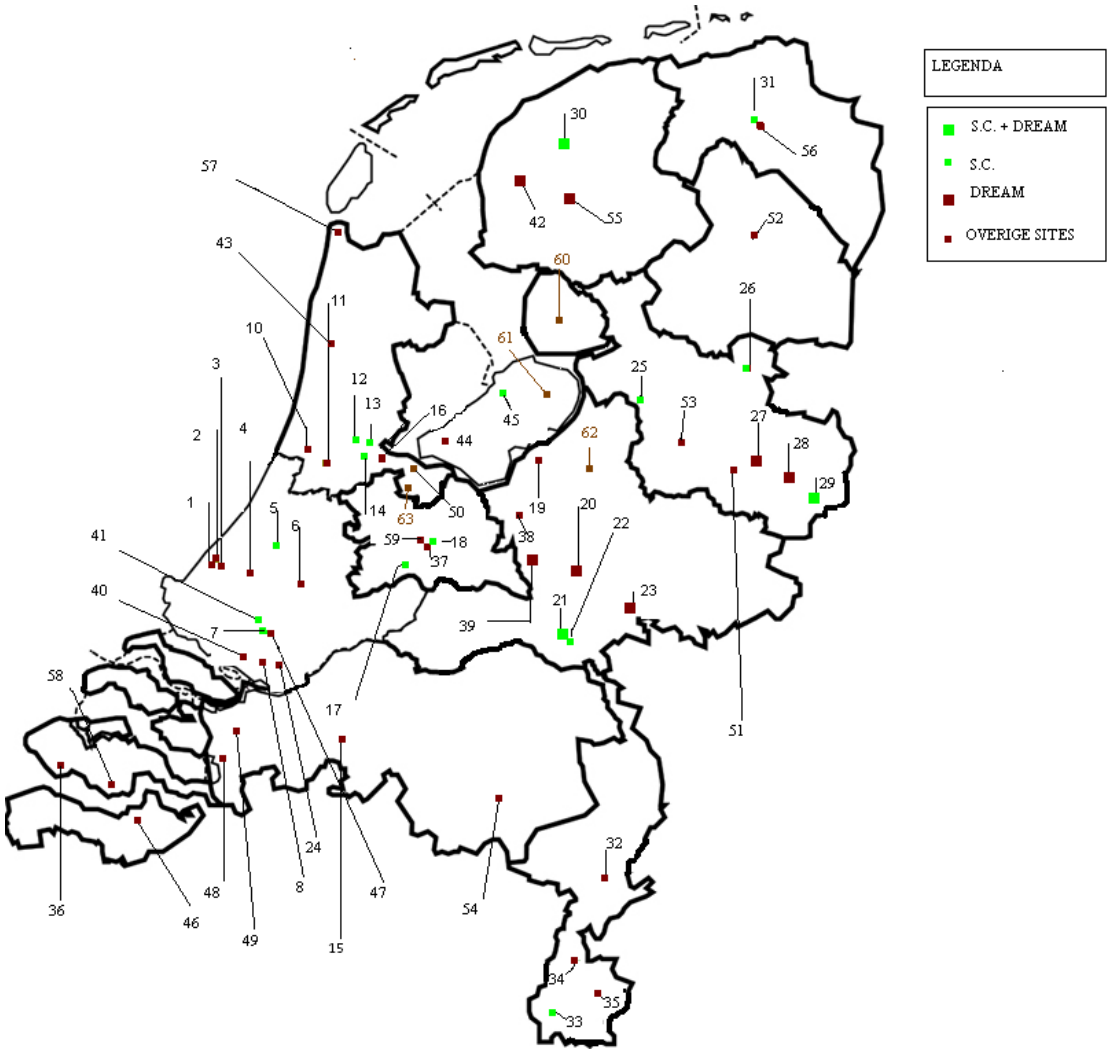
-STOP arm	**2/3**	531 pts = 65%
-CONTINUATION arm	**1/3**	286 pts = 35%

-lost 32 pts

-Every 3 months a check at Outpatient Dpt with joint score

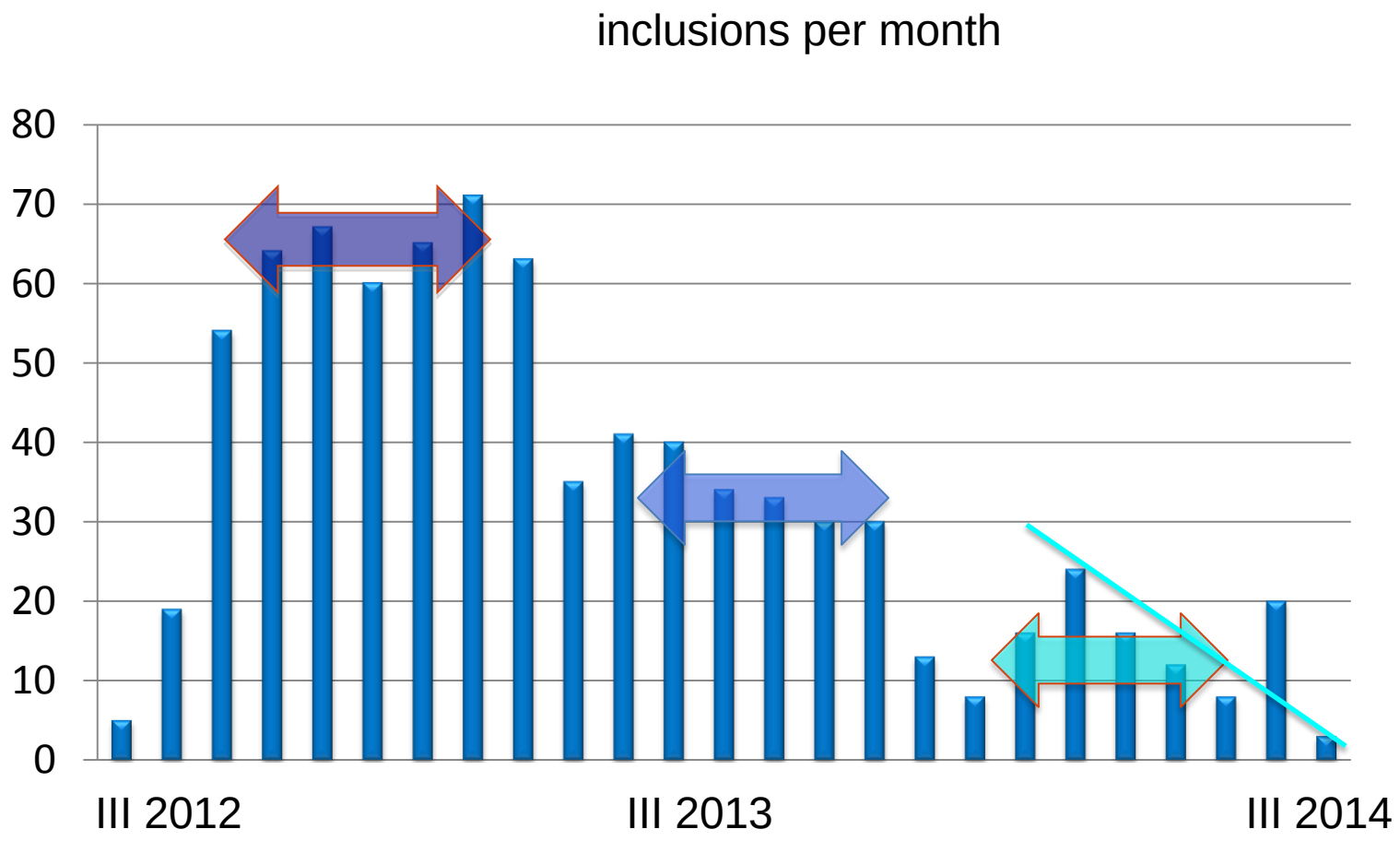
-Endpoint: flare rate = DAS28>3.2 & delta >0.6

POET March 2015 817 pts



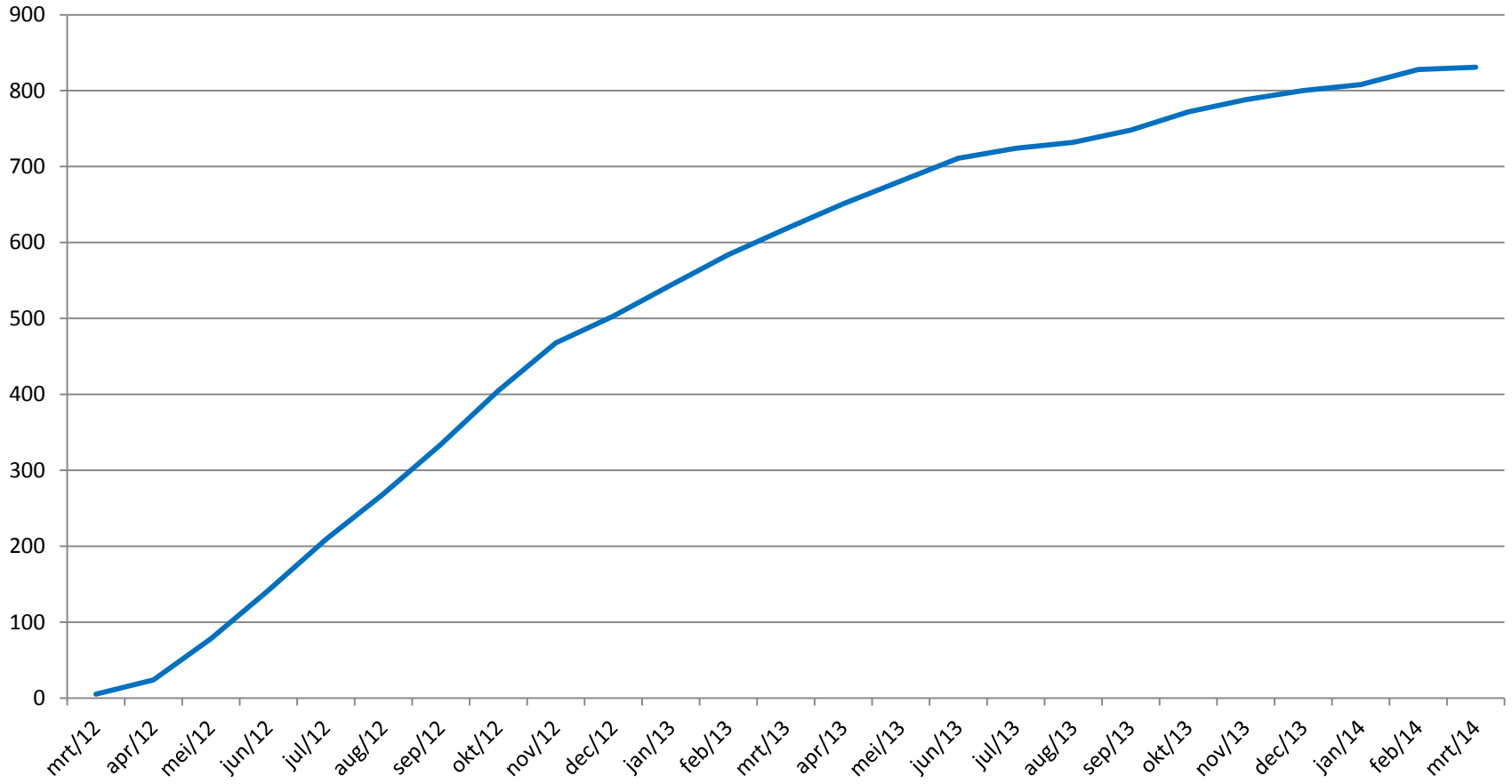
POET

March 2014 817 pts



Inclusion: cumulative

POET



POET – TNFi$_{STOP}$

12 months

Table 1: Baseline characteristics

	Discontinuation group (n=531)	Continuation group (n=286)
Female	362 (68.2%)	188 (65.7%)
Age (years)	59.9 (12.0)	59.7 (10.6)
Disease duration (years)	11.9 (8.8)	11.1 (8.4)
BMI	25.9 (4.3)	26.3 (4.5)
DAS28-ESR	2.08 (0.97)	2.00 (0.80)
RF positive	321 (67.4%)	175 (67.3%)
Anti-CCP positive	324 (68.1%)	176 (67.7%)
Erosive	297 (62.4%)	150 (57.7%)
TNFi		
Adalimumab	271 (51.1%)	129 (45.1%)
Etanercept	213 (40.2%)	133 (46.5%)
Infliximab	25 (4.7%)	14 (4.9%)
Golimumab	15 (2.8%)	8 (2.8%)
Certolizumab	6 (1.1%)	2 (0.7%)
Number of anti-TNF		
1	459 (86.4%)	243 (85.0%)
2	61 (11.5%)	37 (12.9%)
3	10 (1.9%)	6 (2.1%)
DMARD		
MTX	459 (86.4%)	252 (88.1%)
Other DMARD	43 (8.1)%	23 (8.0%)
No DMARD	29 (5.5%)	11 (3.8%)

POET – TNFi$_{STOP}$

12 months

The POET study

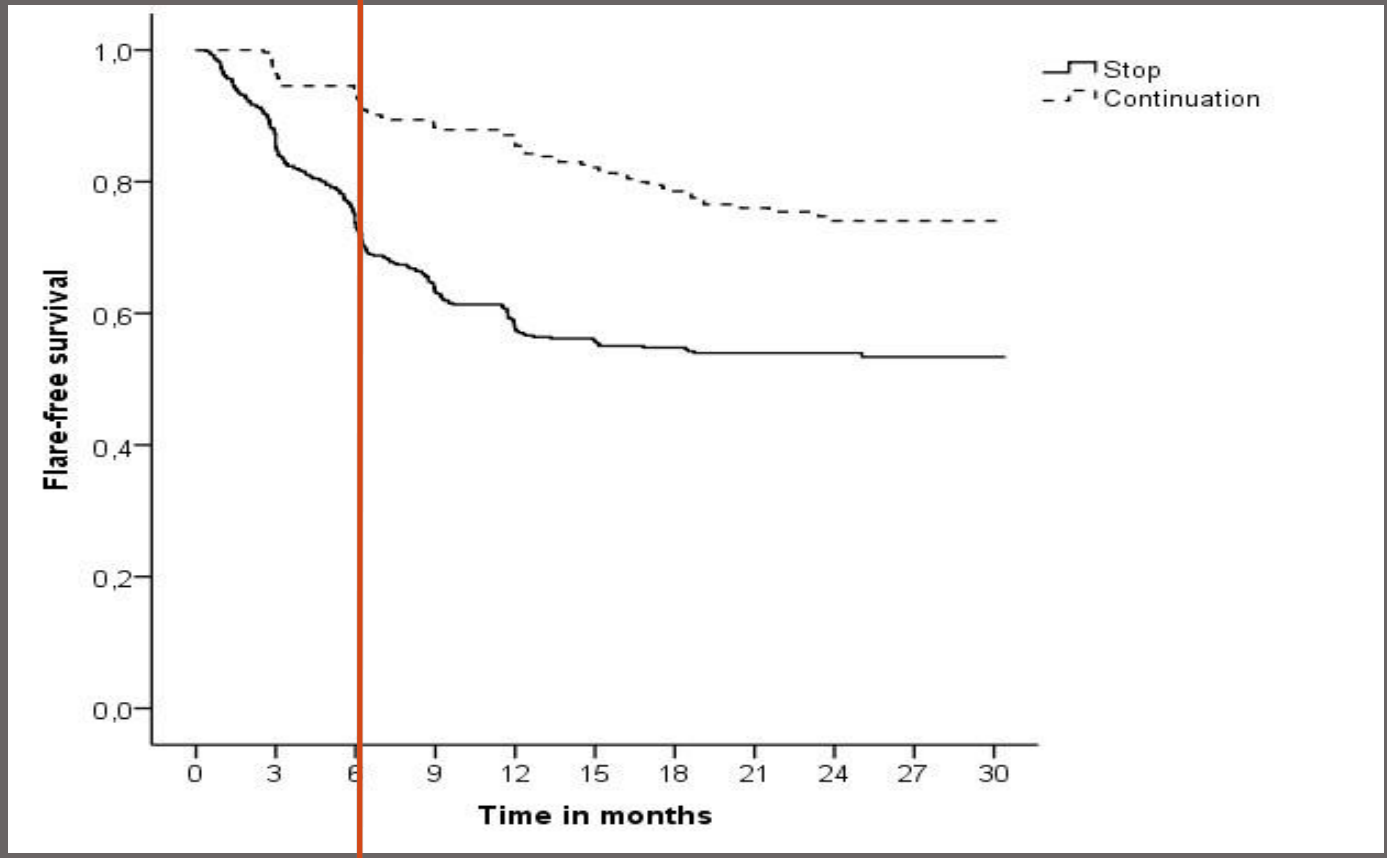
Primary Outcome:		**STOP**	**CONTINUE**	
Flare DAS28	6mos	30.8%	9.4%	p<0.001
	12mos	46.9%	16.6%	p<0.001
Time to 1st Flare		24 wks	38 wks	p<0.001
Flare Free survival	6 mos	74%	93%	
	12mos	58%	86%	
	total	53%	74%	

POET – TNFi$_{STOP}$

Sept 2014 = 6 months

The POET study

Primary Outcome:		**STOP**		**CONTINUE**	
Flare DAS28	6mos	30.8%	3.3	9.4%	p<0.001
	12mos	46.9%	2.8	16.6%	p<0.001
Time to 1st Flare		24 wks		38 wks	p<0.001
Flare Free survival	6 mos	74%		93%	
	12mos	58%		86%	
	total	53%		74%	



Adj HR to flare = 2.46 [1.86-3.25]

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POET – TNFi$_{STOP}$

6 months

Multivariable risk of flare

	Adjusted HR (95% CI)	p value
Female sex	1.34 (1.03–1.75)	0.038
Age (>60 yrs.)	1.06 (0.83–1.35)	0.624
Disease duration (>10 yrs.)	1.19 (0.93–1.52)	0.166
Concomitant DMARD (yes)	0.71 (0.37–1.33)	0.282
Anti-CCP positive	1.04 (0.80–1.34)	0.780
>1 anti-TNF	1.24 (0.89–1.72)	0.197
Discontinuation group	2.42 (1.82–3.23)	<0.001

postflare

TNFi restart after flare	81.3% (243/299)
Identical TNFi at restart	94.7% (230/243)
outcome: LDAS after first flare Complete remission	 78.6% 67.4%

Reported SAE in POET

Stop TNFi 531 pts	Fisher's exact	Continue TNFi 286 pts
5 = 1% 2/3/1	**Traumatic fracture** p=0.17 Cycling/Falling/Collision	0 = 0% 0/0/0
5 = 1% 2/3/0/0	**Infection** Airway/GI / Epidural/ Opportunist	4 = 2% 0/1/1/2
2 = 0.5% 1/0/1	**Malignancy** Bladder/Endometrial/Breast	1 = 0.4% 0/1/0
1 = 0.2% 1/0	**CV event** CVA/myocarial infarct	0 = 0% 0/0
2 = 0.5% 1/1	**Exacerbation of RA** Fatigued/DAS increase	0 = 0%
1 = 0.2% 1/0/0	**Rare** Polyp bleed/radiculopathy/miniMaze	2 = 0.8% 0/1/1

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Potential predictors

Ultrasound: PWD signal

Biomarkers: S100 /12MBDA

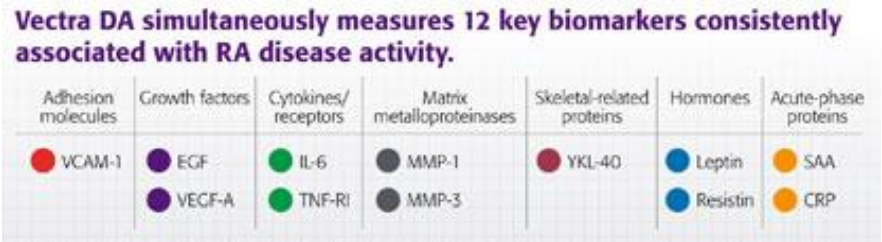
12 MBDA Crescendo:

CRP SAA IL6 TNFR1 MMP1 MMP3

YKL40 Leptin Resistin EGF VEGF VCAM1

Nederlandse Vereniging *voor* Reumatologie

12 MBDA



- VCAM1 adhesion
- EGF growth
- VEGF-A growth
- IL6 cytokine
- TNFR1 cytokine rec
- MMP1 metalloprot
- MMP3 metalloprot
- YKL40 skeletal related
- Leptin satiety hormone
- Resistin hormone
- SAA acute phase
- CRP acute phase

	T up to 3 months	T up to 6 months	T up to 12 months
CRP	1.04 (1.01-1.08) p=0.015	1.03 (0.99-1.06) p=0.13	1.00 (0.97-1.03) p=0.99
SAA	0.94 (0.86-1.02) p=0.14	1.00 (0.94-1.07) p=0.89	1.03 (0.96-1.11) p=0.40
IL6	1.02 (1.00-1.03) p=0.012	1.01 (1.00-1.02) p=0.19	1.01 (0.99-1.03) p=0.18
TNFR1	0.77 (0.37-1.63) p=0.49	1.01 (0.51-2.02) p=0.98	1.15 (0.55-2.40) p=0.72
MMP1	0.94 (0.96-1.04) p=0.77	0.98 (0.94-1.01) p=0.16	0.96 (0.93-1.00) p=0.035
MMP3	1.01 (0.99-1.03) p=0.15	1.01 (0.99-1.03) p=0.08	1.01 (0.995-1.03) p=0.19
YKL40	0.99 (0.99-1.00) p=0.32)	0.998 (0.996-1.000) p=0.08	0.998 (0.997-1.000) p=0.10
Leptin	1.01 (0.99-1.02) p=0.54	1.00 (0.99-1.01) p=0.96	1.01 (1.00-1.03) p=0.14
Resistin	1.00 (0.92-1.09) p=0.99	1.03 (0.96-1.11) p=0.40	1.08 (1.00-1.17) p=0.04
EGF	0.998 (0.996-1.002) p=0.11	1.00 (0.995-0.999) p=0.003	0.997 (0.995-0.999) p=0.002
VEGF	0.99 (0.99-1.00) p=0.33	1.00 (0.998-1.001) p=0.43	1.00 (0.998-1.001) p=0.31
VCAM1	2.64 (0.57-12.18) p=0.21	1.36 (0.34-5.51) p=0.66	2.11 (0.49-9.02) p=0.31

Odds ratios at T0 for clinical flare in 439 LDA RA pts stopping TNFi

N flare/total N Odds (Chi square) P value	T 3 months	T 6 months	T 9 months	T 12 months
Flare/BFR based on DAS28	66/373 1.00 (0.98 – 1.02) p=0.86	117/322 1.01 (0.99-1.02) p=0.34	158/281 1.01 (0.99-1.02) p=0.39	180/259 1.01 (1.00-1.03) p=0.15
Clinical Flare	118/321 1.02 (1.01-1,04) p=0.009	197/242 1.025 (1.01-1.04) p=0.002	234/205 1.017 (1.00-1.03) p=0.025	246/193 1.02 (1.01-1.04) p=0.004
+1 SJC	129/310 1.01 (0.99-1.-3) p=0.27	207/232 1.01 (1.00-1.03) p=0.21	242/197 0.01 (1.00-1.03) p=0.18	269/170 1.01 (1.00-1.03) p=0.13
ESR>20&CRP>12	39/400 1.07 (1.04-1.10) p<0.001	63/376 1.06 (1.03-1.08) p<0.001	73/366 1.05 (1.03-1.07) p<0.001	80/359 1.05 (1.03-1.07) p<0.001

Odds ratios for 4 flare definitions in 439 LDA RA pts stopping TNFi at T0

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POET – TNFi$_{STOP}$

12 months in all 817

1-BFR is feasible in 50%

2-TNFi added to csDMARD is a highly potent antirheumatic bridging option as TNFi stopping is feasible:
-If male & deep remission for longer period of time: no PDS
-Irrespective of ACPA positivity
-With green signals: low IL6 / MMP1/ 12BMDA

3-TNFi restarting is a safe and effective therapeutic option

4-Further analysis needed for existing Qs upon predictors

Acknowledgements for the POET

All 817 RA patients committed to POET		F Lamers; M Ghiti
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ROMA ICT		HE Vonkeman / P ten Klooster
NVR Board		B Dijkmans/GA van Albada/ H Moens/ R Landewe
Patients' Society		G Willemsen
ZonMW/Ministry of Health		B Vingerhoeds-van Aken/ H Kooijman

Nederlandse Vereniging voor Reumatologie

Participating centres

- Medisch Spectrum Twente Enschede;
- Ziekenhuisgroep Twente Hengelo / Almelo;
- Rijnstate Ziekenhuis Arnhem Arnhem;
- Isala klinieken Zwolle Zwolle;
- Universitair Medisch Centrum Groningen Groningen;
- TweeSteden ziekenhuis Tilburg Tilburg;
- Radboud UMC Nijmegen Nijmegen;
- St. Maartenskliniek Nijmegen;
- Medisch Centrum Leeuwarden Leeuwarden;
- Antonius Ziekenhuis West Friesland Sneek;
- Leids Universitair Medisch Centrum Leiden;
- Ziekenhuis Gelderse Vallei Ede;
- Academisch Ziekenhuis Maastricht Maastricht;
- Medisch Centrum Parkstad Heerlen;
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- Flevoziekenhuis Almere;
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- Tergooiziekenhuizen Hilversum;
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- Gelre Ziekenhuis Apeldoorn/Zuthpen;
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- Amphia Ziekenhuis Breda;
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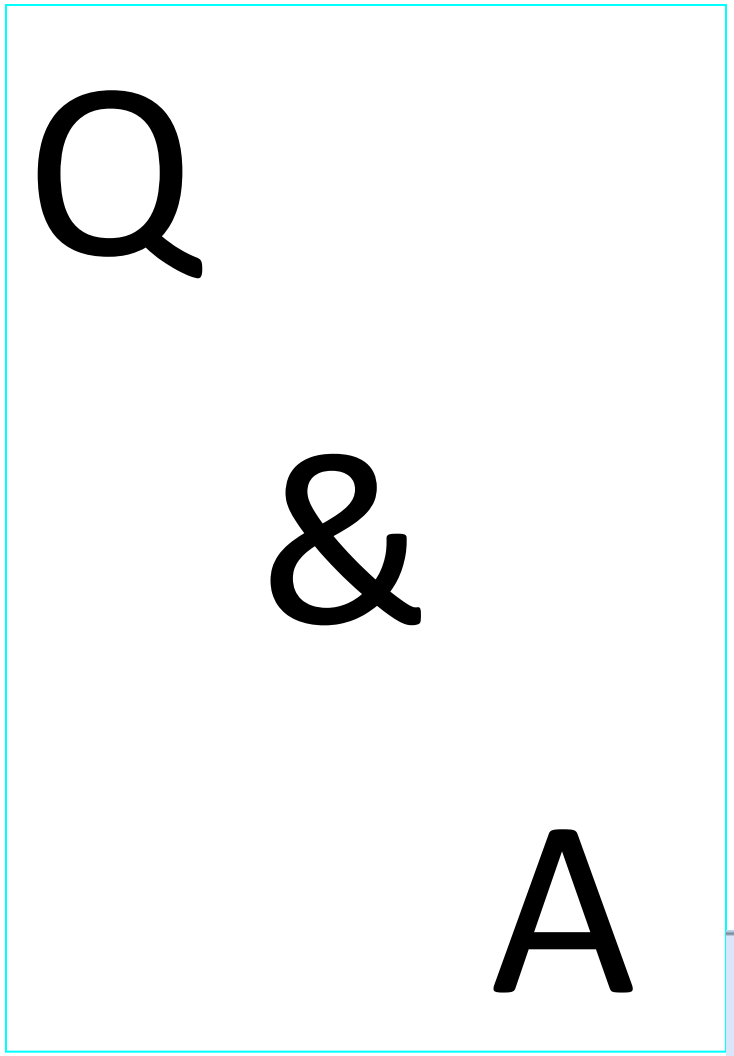
thank you for your attention



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