Diagnosis and Management of Takayasu Arteritis

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Disclosures

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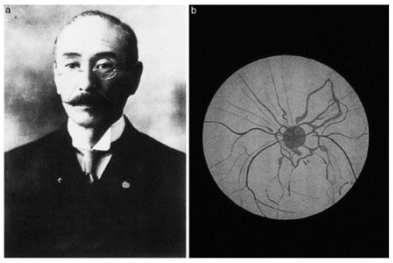
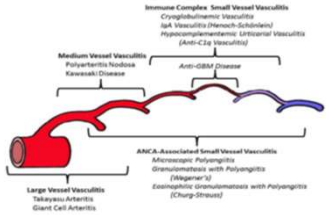
  - ***Roche, Abbvie, Amgen, MSD, Pfizer, BMS, UCB, Cellgene***



Outline

- Diagnosis and Classification
- Assessment
- Management



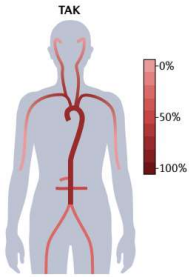
Takayasu Arteritis (TAK)

- **Granulomatous arteritis predominantly affecting the aorta and/or its major branches** ***(Chapel-Hill, 2012)***
  - ***No involvement of small vessels***
- **Onset usually < 50 years, with female dominance (F/M: 5-9/1)**
- **Incidence: 0.5-3.4/million, Prevalence: 8-40/million**
- ***Most common in East Asia (India, Japan, Korea) - Frequency in Middle-Eastern races ?***

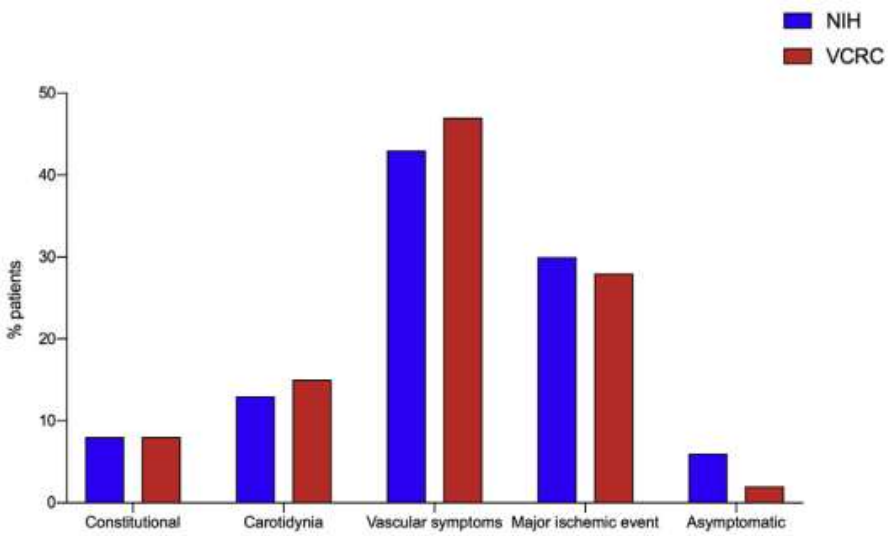
(Watts R, Nat Rev Rheumatol, 2022)

- **A slow, progessive disease course with increased mortality**

Red Flags and Symptoms in TAK



- An unexplained acute phase response (raised erythrocyte sedimentation rate or C-reactive protein levels, or both)
- Carotidynia
- Hypertension
- Discrepant blood pressure between the arms (>10 mmHg)
- Absent or weak peripheral pulse(s)
- Limb claudication
- Arterial bruit
- Angina

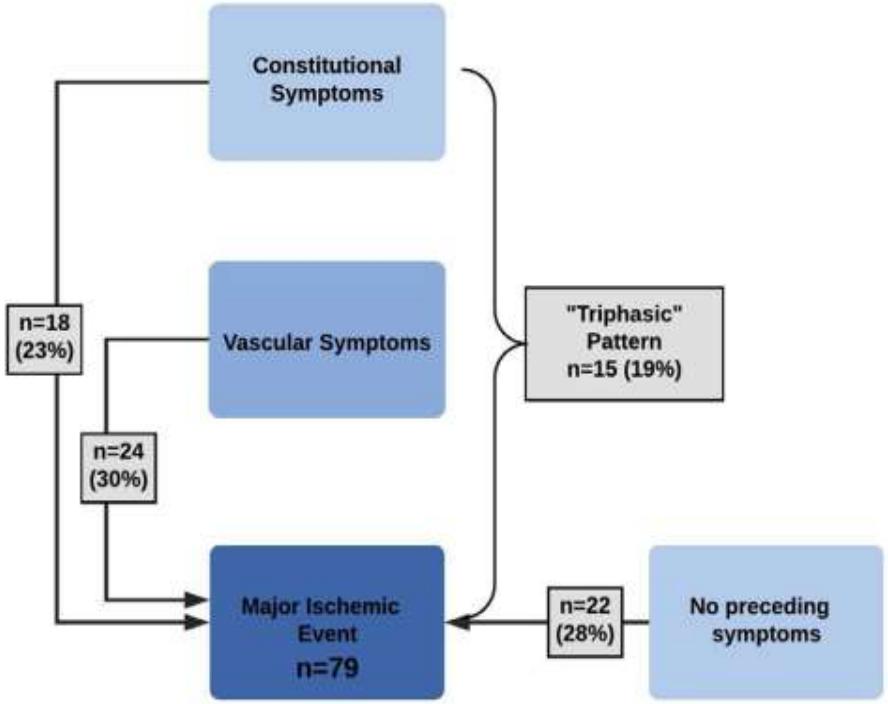


(Mason J, Nat Rev Rheum, 2010)

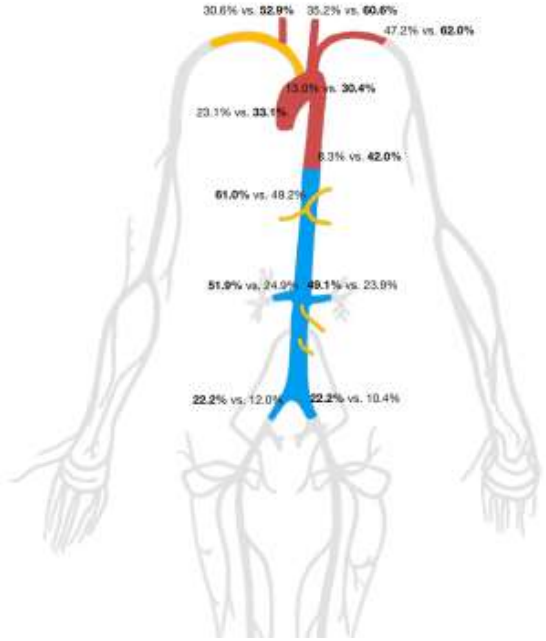
(Quinn K, Sem Arth Rheum, 2020)

Patterns of Clinical Presentation in Takayasu's Arteritis

A 'triphasic' disease



(Quinn K, Sem Arth Rheum, 2020)



(Tomelleri A, Scan J Rheumatol, 2019)

Early-diagnosed Takayasu has more inflammation, less damage

- Early diagnosis TAK patients (last 24 months) followed as an 'Inception Cohort' in Turkey

	Inception Cohort (n=166) (%)	Retrospective Cohort (n=248) (%)
Constitutional	70	66
Limb claudication	79	48
Carotidynia	25	6
Mucocutaneous	21	9
Pulseless	35	88
Type I (Limited disease)	68	32
Type V (whole aorta)	20	51

(Bıçakçıgil M, Clin Exp Rheum, 2009)
(Alibaz-Oner F,unpublished)

eular

EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update

(Dejaco C, Ann Rheum Dis, 2023)

- **In patients with suspected TAK, MRI should be used as the first imaging test to make a diagnosis of TAK**
  - ***to investigate mural inflammation and/or luminal changes***
- **FDG-PET, CT or ultrasound may be used as alternative imaging modalities**
- **Conventional angiography is not recommended for the diagnosis of TAK**
  - ***except intra-vascular interventions are planned***

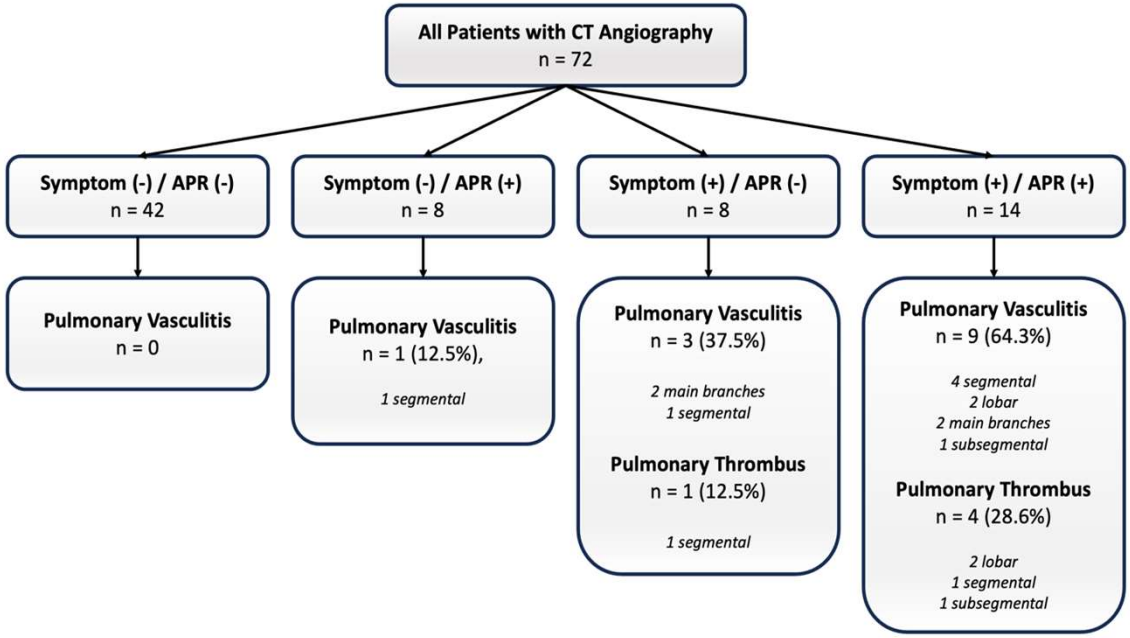
Pulmonary Involvement in TAK

- **Pulmonary arterial involvement: 6-19 %**
  - **Associated with clinical activity**
- **Pulmonary arterial hypertension: 0-18 %**
  - **Differentiation from secondary causes is necessary**
    - **ventricular enlargement, valve regurgitations and congestive heart failure**
- **Mortality: PAI: 9-21 %, PAH: 8-33 %**

(Toledano, Sem Arthritis Rheum, 2011, Direskeneli H, Int J Cardiology, 2018)

Pulmonary symptoms and acute-phase response is higher in patients with pulmonary vasculitis in TAK

- 72 patients, pulmonary vasculitis: 18 %



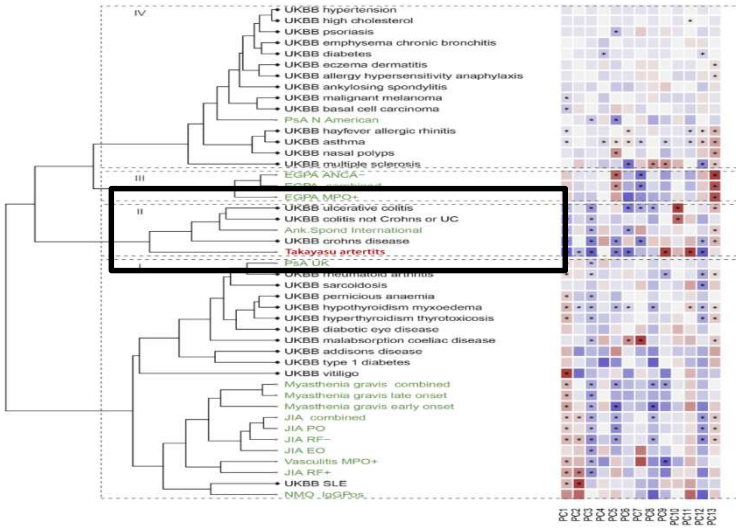
(Sevik G, Vasculitis2024, abst)

Takayasu's Arteritis associated inflammatory diseases

clues from the genetics

- GWAS with 1226 patients - 5 ethnicities

- Turkish, North European, Italian, South Asian, Chinese



(Ortiz-Fernandez L.. Sawalha AH, AJHG, 2021)

- Inflammatory BP/axial SpA: 7-20 %

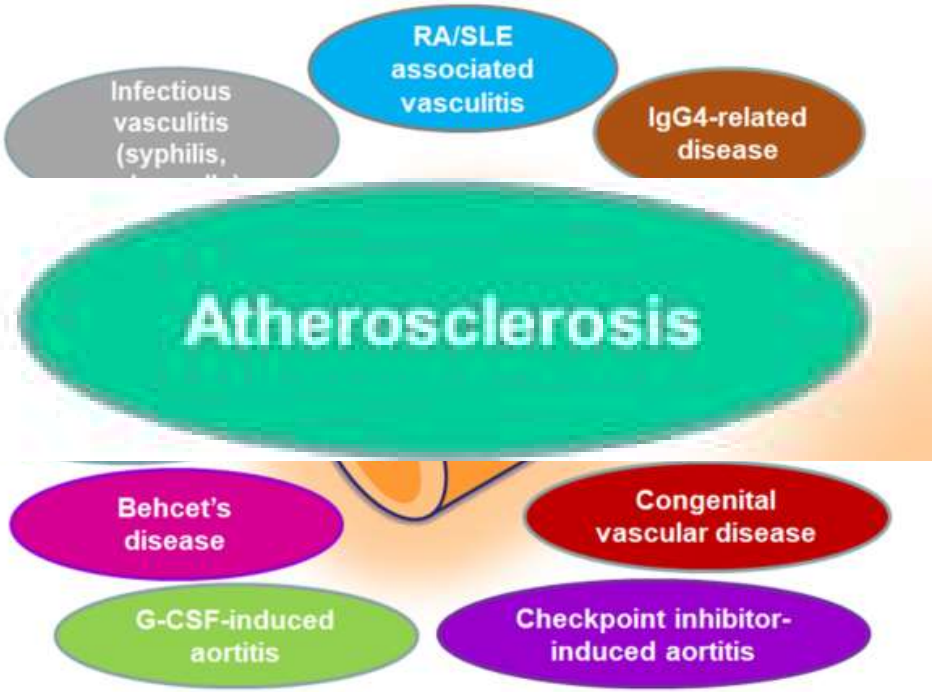
- Inflammatory bowel disease: 3-9 %

- Psoriasis: 1-4 % - E. Nodosum: 2-4 %

- Associated with early onset and biologic use

(Abacar K, Joint B Spine, in press)

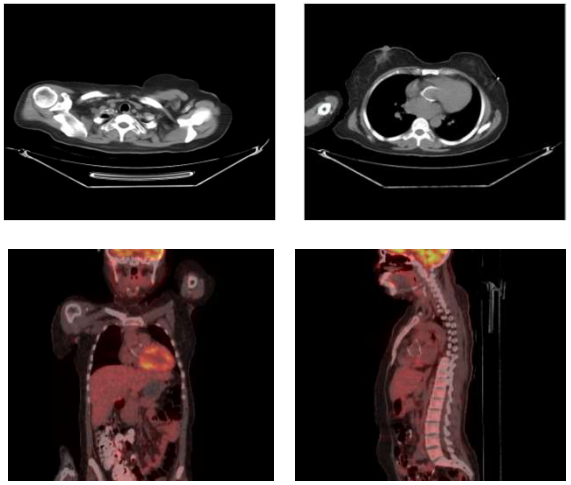
Mimics of Large-vessel Vasculitis



(Watanabe R, Current Rheum Rep, 2020)

Differential Diagnosis: Accelerated Atherosclerosis vs TAK ?

- 35, female with dizziness and chest pain
- A bruit on right subclavian artery
- Right CCA stenosed, bilateral ICA occluded
- Extensive coronary involvement
- CRP: 8 mg/L
- Smoker with hyperlipidemia



	Atherosclerosis	Takayasu
Stenosis	Bifurcations/ostiums	Proximal arteries
Aneurysms	Abdominal	Thoracic
PET-CT	localized hot spots	linear diffuse
CT	linear calcifications	
	discrete plaque lesions	

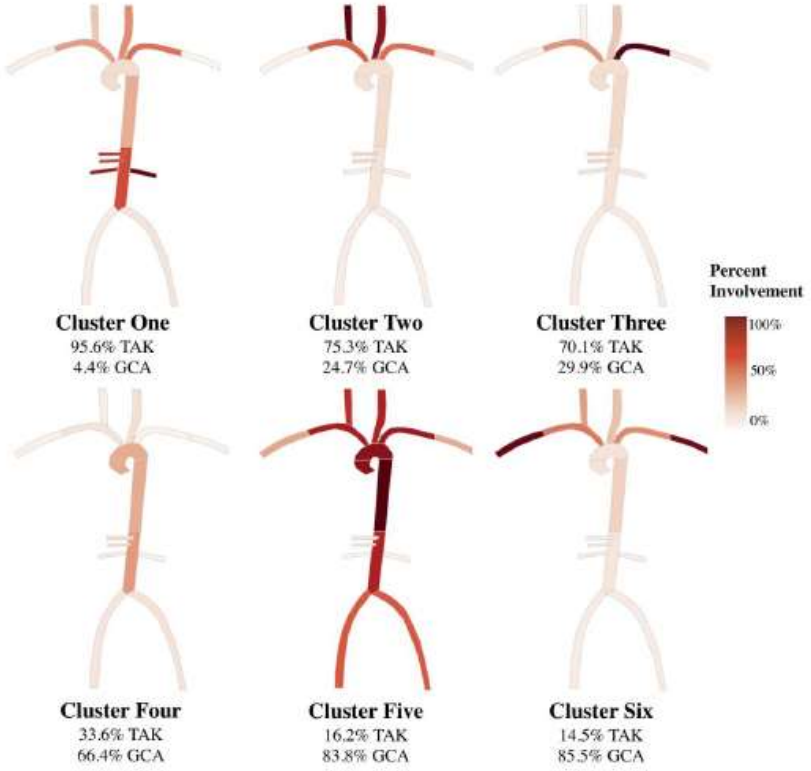
- Presence of traditional cardiovascular risk factors
  - *Involvement of ilio-femoral arteries in PET/CT is associated with older age, male gender and smoking*

(Kaymaz-Tahra T, unpublished)

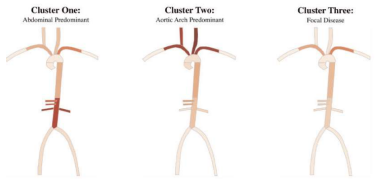
Angiographic clusters in TAK and GCA

Table 1. Frequency of arterial involvement by cluster in the DCVAS cohort

	Cluster 1 n=92	Cluster 2 n=150	Cluster 3 n=144	Cluster 4 n=166	Cluster 5 n=65	Cluster 6 n=61
% Takayasu's arteritis	90 (95.6)	130 (75.3)	120 (70.1)	86 (33.6)	19 (16.2)	16 (14.5)
% Giant cell arteritis	2 (4.4)	20 (24.7)	24 (29.9)	80 (66.4)	46 (83.8)	45 (85.5)
Descending Aorta	26 (28.3)	21 (14.0)	21 (14.6)	49 (29.5)	65 (100)	10 (16.4)
Abdominal Aorta	54 (58.7)	14 (9.3)	15 (10.4)	58 (34.9)	48 (73.8)	5 (8.2)
Left Axillary	0 (0.0)	8 (5.3)	7 (4.9)	3 (1.8)	19 (29.2)	57 (93.4)
Right Axillary	3 (3.3)	3 (2.0)	4 (2.8)	5 (3.0)	20 (30.8)	59 (96.7)
Left Carotid	36 (39.1)	130 (86.7)	30 (20.8)	20 (12.0)	48 (73.8)	14 (23.0)
Right Carotid	19 (20.7)	147 (98.0)	2 (1.4)	7 (4.2)	45 (69.2)	21 (34.4)
Mesenteric	60 (65.2)	23 (15.3)	24 (16.7)	21 (12.7)	5 (7.7)	3 (4.9)
Left Renal	90 (97.8)	6 (4.0)	9 (6.3)	3 (1.8)	1 (1.5)	2 (3.3)
Right Renal	77 (83.7)	5 (3.3)	13 (9.0)	7 (4.2)	0 (0.0)	3 (4.9)
Left Subclavian	44 (47.8)	74 (49.3)	144 (100.0)	1 (0.6)	53 (81.5)	24 (39.3)
Right Subclavian	31 (33.7)	79 (52.7)	53 (36.8)	15 (9.0)	50 (76.9)	28 (45.9)



(Gribbons KB, Arth Care Res, 2019)

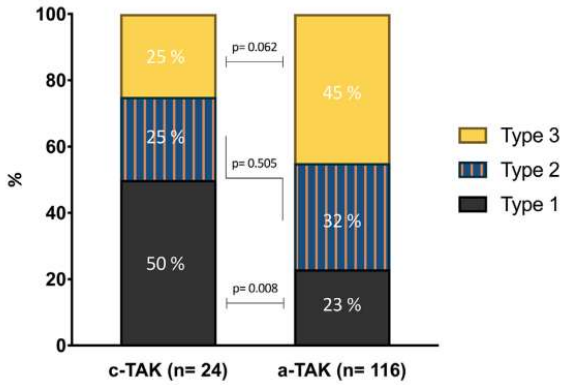


Clusters and Clinical Course in TAK

Cluster Prevalence by Country

	India (n = 581)	N. America (n = 225)	Turkey[1,2] (n = 421)
Cluster One	236 (40.6)	53 (23.6)	90 (21.4)
Cluster Two	159 (27.4)	79 (35.1)	148 (35.2)
Cluster Three	186 (32.0)	93 (41.3)	183 (43.5)

[1]p < .01 vs. India and [2]p = .79 vs. North America



(Karabacak M, Sem Arth Rheum, 2021)

- **Rare change in clusters:**
  - ***1 % during 3.3 years (N. American), 13 % in 5 years (Turkish) of follow-up***
- **Associated with relapses ?**
  - ***'Sustained clinical remission' less and biologic use more common in cluster II***

(Goel R, 2020 - Gribbons KB, ACR2021)

ACR 1990 TAK Classification Criteria

- **Age at disease onset < 40 years**
- **Claudication of extremities**
- **Decreased brachial artery pulse**
- **BP difference in extremities: > 10 mm Hg**
- **Bruit over subclavian arteries or aorta**
- **Arteriogram abnormality**

- 3/6 criteria

- Sensitivity: 90.5% - Specificity: 97.8%

(Arend WP, Arthritis Rheum, 1990)

- **In DCVAS Registry**

- Sensitivity: 73.6% - Specificity: 98.3%

(*Seeliger B, Rheumatology, 2017)*

Arthritis & Rheumatology
Vol. 0, No. 0, Month 2022, pp 1–9

2022 American College of Rheumatology/EULAR Classification Criteria for Takayasu Arteritis

Peter C. Grayson,[1] Cristina Ponte,[2] Ravi Suppiah,[3] Joanna C. Robson,[4] Katherine Bates Gribbons,[1] drew Judge,[5] Anthea Craven,[6] Sara Khalid,[6] Andrew Hutchings,[7] Debashish Danda,[8] ashid A. Luqmani,[6] Richard A. Watts,[9] and Peter A. Merkel[10], for the DCVAS Study Group

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify the patient as having Takayasu arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

ABSOLUTE REQUIREMENTS

Age ≤ 60 years at time of diagnosis	
Evidence of vasculitis on imaging[1]	

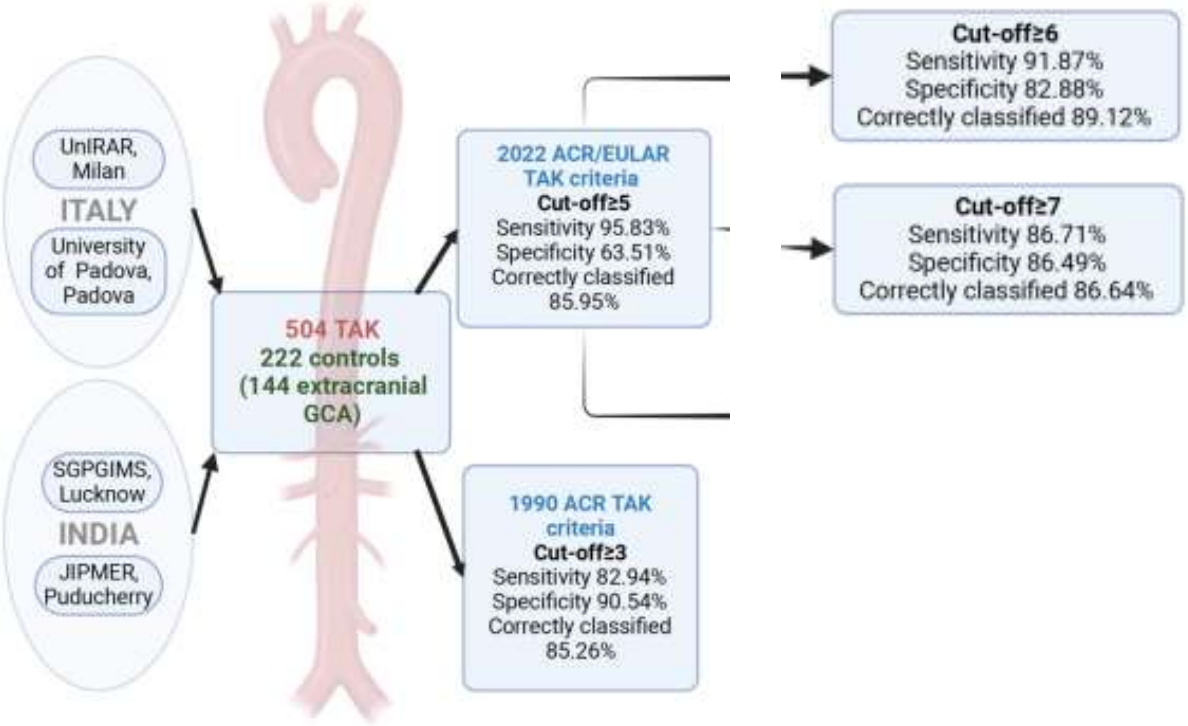
ADDITIONAL CLINICAL CRITERIA

Female sex	+1
Angina or ischemic cardiac pain	+2
Arm or leg claudication	+2
Vascular bruit[2]	+2
Reduced pulse in upper extremity[3]	+2
Carotid artery abnormality[4]	+2
One arterial territory	+1
Two arterial territories	+2
Three or more arterial territories	+3
Symmetric involvement of paired arteries[6]	+1
Abdominal aorta involvement with renal or mesenteric involvement[7]	+3

Sum the scores for 10 items, if present. A score of ≥ 5 points is needed for the classification of TAKAYASU ARTERITIS.

Patient subset	Total no patients (no TAK patients)	Sensitivity (95% CI)	Specificity (95% CI)
Development data set	639 (316)	89.9 (86.0 to 93.0)	96.6 (94.0 to 98.3)
Validation data set	273 (146)	93.8 (88.6 to 97.1)	99.2 (96.7 to 100.0)

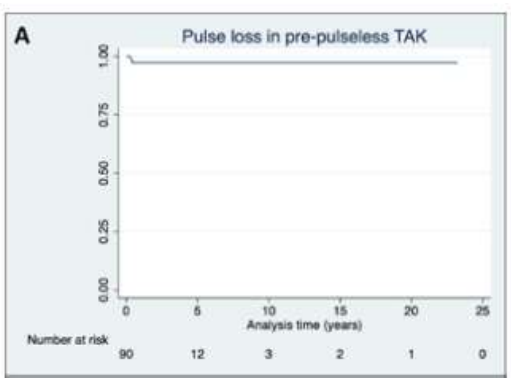
Validation of the 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis

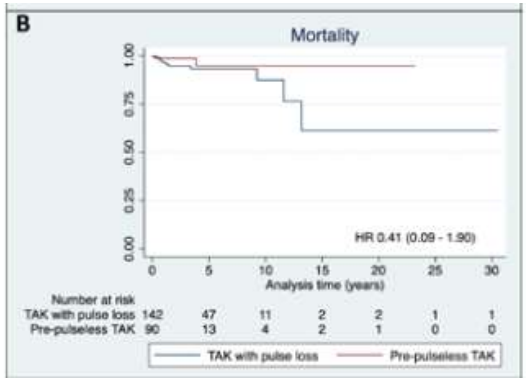


(Tomelleri A, Rheumatology, 2023)

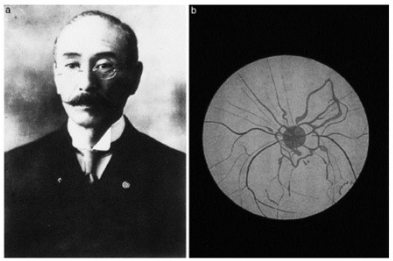
TAK patients without pulse-loss fullfill new criteria better

	Pre-pulseless TAK (n=91)	TAK with pulse loss (n=147)	p value*
Duration of follow-up (months) (Mean ± SD)	34.86 ± 43.86	47.62 ± 51.56	0.051
Fulfilled 1990 ACR classification criteria [n(%)]	73 (80.22%)	144 (97.96%)	**<0.001**[b]
Number of items fulfilled on the 1990 ACR classification criteria (Mean ± SD)	3.55 ± 1.23	4.56 ± 1.02	**<0.001**
Fulfilled 2022 ACR/EULAR classification criteria [n(%)]	84 (92.31%)	144 (97.96%)	**0.047**[b]





(Misra DP, Med J Rheumatol, 2023)



Outline

- Diagnosis and Classification
- *Assessment*
- Management

Composite approach to assess disease activity in TAK

- **NIH Definition (any 2):** *(Kerr GS, Ann Int Med, 1994)*

- Onset or worsening of

  - **Presence of systemic signs or symptoms not attributable to any other condition**
  - **Signs or symptoms of vascular insufficiency**
    - ***Claudication, diminished or absent pulse, bruit, vascular pain, asymmetric blood pressure (BP) in extremities***
  - **Elevation of ESR or CRP without infection or malignancy**
  - **New vascular lesions in imaging**

- **Used in >60 % of the studies in the literature**

(Direskeneli H, J Rheumatol, 2011)

2021 ACR/VCRC Guideline for the Management of GCA and TAK

Recommendation	TAK PICO question informing recommendation and discussion	Level of evidence
Clinical/laboratory monitoring		
Recommendation: For patients with TAK, we conditionally recommend adding inflammation markers to clinical monitoring as a disease activity assessment tool.	2	Very low to low
Recommendation: For patients with TAK in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.	4	Very low
Recommendation: For patients with TAK in apparent clinical remission but with an increase in levels of inflammation markers, we conditionally recommend clinical observation without escalation of immunosuppressive therapy.	19	Very low

(Maz M, Arthritis Rheumatol 2021)

Monitorization with imaging in Guidelines

- **In case of a suspected relapse of TAK, particularly when laboratory markers of disease activity are unreliable, ultrasound, FDG-PET or alternatively MRI may be considered for the assessment of vessel abnormalities.**
  - ***MR, CT or US for long-term monitoring of structural damage***

- **Imaging is <u>not routinely recommended</u> for patients in clinical and biochemical remission.**

  - Level of Evidence: 5 ***(Dejaco C, Ann Rheum Dis, 2023)***

- **<u>Regularly scheduled</u> non-invasive imaging is <u>conditionally recommended</u> in addition to routine clinical assessment in patients with TAK.**

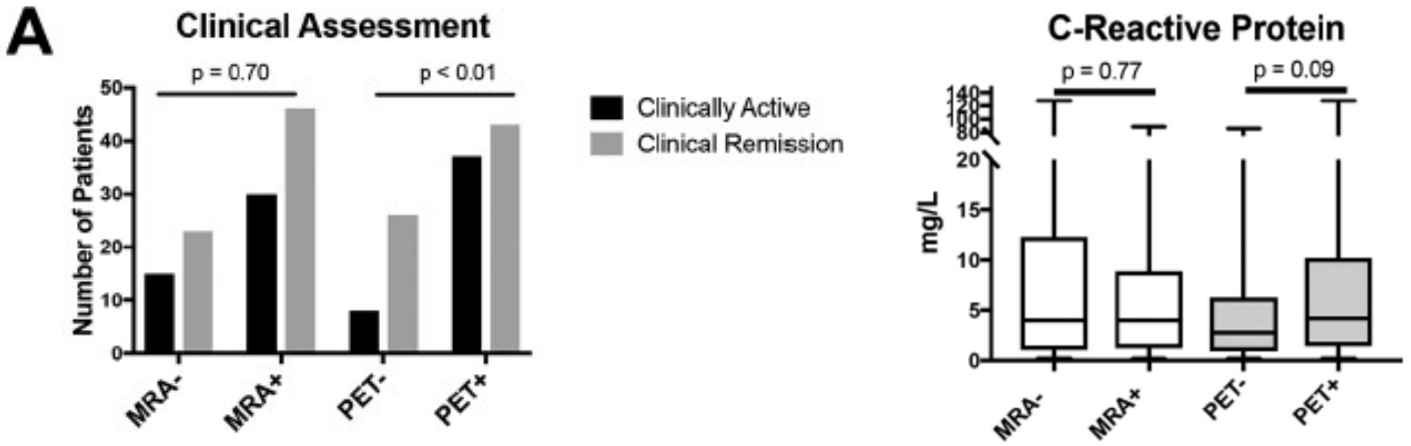
  - Very low/low evidence

  (Maz M, Arthritis Rheumatol, 2021)

Comparison of magnetic resonance angiography and ^{18}F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis

Kaitlin A Quinn,[1,2] Mark A Ahlman,[3] Ashkan A Malayeri,[3] Jamie Marko,[3] Ali Cahid Civelek,[3] Joel S Rosenblum,[2] Armin A Bagheri,[2] Peter A Merkel,[4] Elaine Novakovich,[2] Peter C Grayson[2]

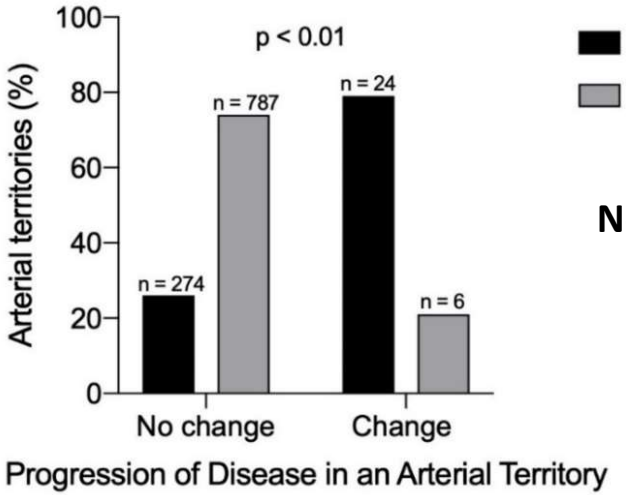
Ann Rheum Dis 2018;**0**:1–7.



- 94% of patients with active disease and 78% of patients in clinical remission had activity in MRI or PET (or both)

‘Angiographic progression’ is very low in TAK especially in vascular areas with no PET activity at baseline

- 70 pts with LVV (TAK: 38, GCA: 32)



No arterial change in 97.3 % (1061/1091) in 1.6 years of follow-up

- ***1 % change if no baseline damage***
- ***9 % change with baseline involvement***

(Quinn K, Arth Rheumatol 2022, art.42290)

TAIDAI (Takayasu's Arteritis Integrated Disease Activity Index) Scoring Sheet

- **Each symptom was paired with PET findings in corresponding arterial territories Constitutional symptoms were paired with APR levels**
- **One point was given for each clinical symptom paired with supporting FDG-PET or laboratory abnormalities and summed into the TAIDAI score**
- **A TAIDAI of ≥1 defined active disease**

	Step One: Check if clinical symptom present within 7 days of evaluation →	Step Two: Check if active vasculitis by imaging or labs (FDG uptake in arterial territory > liver by inspection) →	Step Three: 1 pt each
1.	☐ Left carotidynia	☐ Left Carotid	☐
2.	☐ Right carotidynia	☐ Right Carotid	☐
3.	☐ Left arm claudication	☐ Left Subclavian or Left Axillary	☐
4.	☐ Right arm claudication	☐ Right Subclavian or Right Axillary	☐
5.	☐ Left leg claudication	☐ Left Iliofemoral or Abdominal Aorta	☐
6.	☐ Right leg claudication	☐ Right Iliofemoral or Abdominal Aorta	☐
7.	☐ Left frontotemporal headache	☐ Left Carotid	☐
8.	☐ Right frontotemporal headache	☐ Right Carotid	☐
9.	☐ Left posterior headache / neck pain	☐ Left Vertebral	☐
10.	☐ Right posterior headache / neck pain	☐ Right Vertebral	☐
11.	☐ Vertigo or lightheadedness	☐ Left or Right Vertebral or Left or Right Carotid	☐
12.	☐ Visual disturbance	☐ Left Carotid or Right Carotid	☐
13.	☐ Jaw claudication	☐ Left Carotid or Right Carotid	☐
14.	☐ Back pain	☐ Thoracic or Abdominal Aorta	☐
15.	☐ Ischemic chest pain	☐ Thoracic Aorta	☐
16.	☐ Ischemic abdominal pain	☐ Abdominal Aorta or Mesenteric	☐
17.	☐ Constitutional symptoms	☐ CRP ≥ 10mg/L or ESR ≥ 40 mm/hr	☐
		Total TAIDAI Score *sum all Items from Step Three*	☐

(Marvisi C, Arth Care Res, 2024)

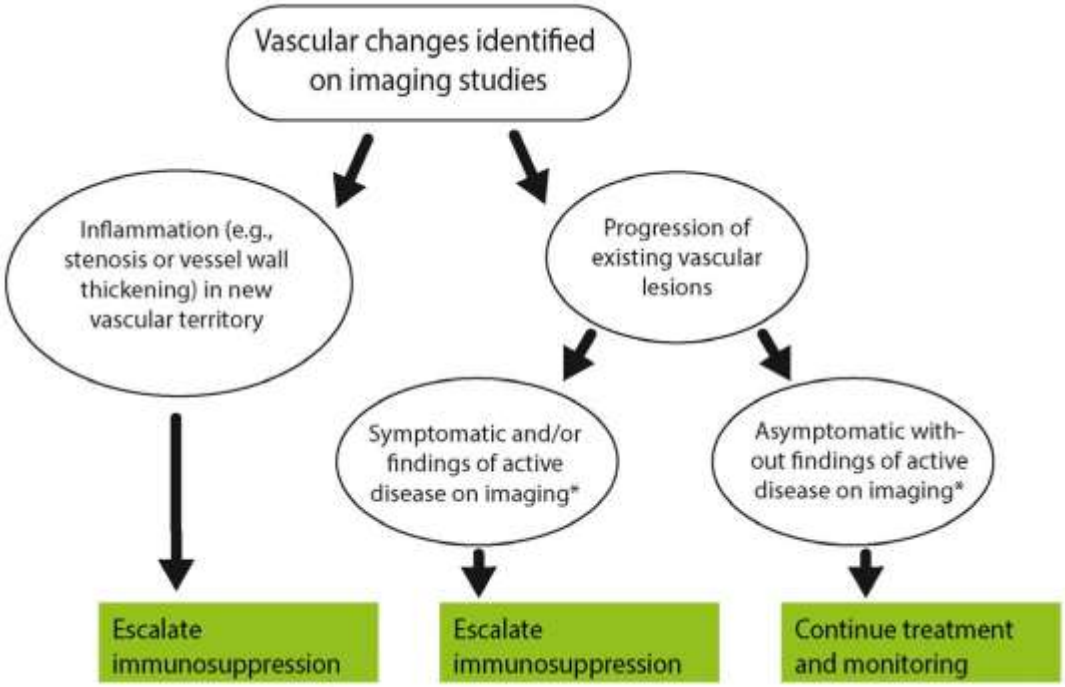
TAIDAI has good correlation with disease activity scores

	By variable	*P* value	Spearman's ρ
TAIDAI	PhGA	<0.0001[a]	0.5523
TAIDAI	PETVAS	<0.0001[a]	0.4742
PETVAS	PhGA	<0.0001[a]	0.3686
TAIDAI	CRP	<0.0001[a]	0.3128
TAIDAI	PtGA	0.0002[a]	0.3026
ESR	PhGA	0.0003[a]	0.2535
ESR	PtGA	0.0076[a]	0.2158
PtGA	PhGA	0.0110[a]	0.2058
TAIDAI	ESR	0.0043[a]	0.1991

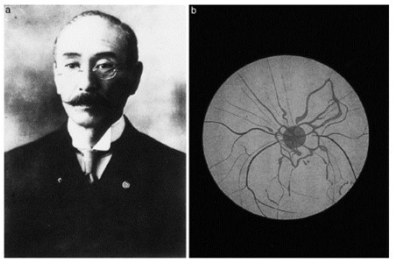
- **TAIDAI has 96 % sensitivity and 79 % specificity compared to PhGA**
- **In patients treated with TNF inhibitors or Tocilizumab TAIDAI=0 was achieved in 91 %**

(Marvisi C, Arth Care Res, 2024)

Vascular changes in imaging:
Escalation vs continuing treatment ?



(Maz, Arthritis Rheumatol, 2021)



Outline

- **Diagnosis and Classification**
- **Assessment**
- ***Management***

Management - EULAR 2018

- **All patients presenting with signs and symptoms suggestive of Takayasu's arteritis should be referred to a specialist team for multi-disciplinary diagnostic work-up and management.**
  - ***Rheumatologist, cardiologist, cardiovascular surgeon, neurologist, radiologist etc.***

- **For remission induction: glucocorticoids (40-60 mg/d prednisolone)**

  (Strength of recommendation: D, EULAR Recommendations, ARD, 2019)
  - **Tapering to < 10 mg/d in one year**

- **Non-biologic DMARDs should be given to all patients with GCs**

  - Azatioprine, methotrexate, cyclophosphamide, leflunomide, mycophenolate mophetil

  (Strength of recommendation: C)
- **Tocilizumab or TNF inhibitors can be considered in relapsing disease**

  (Strength of recommendation: C)

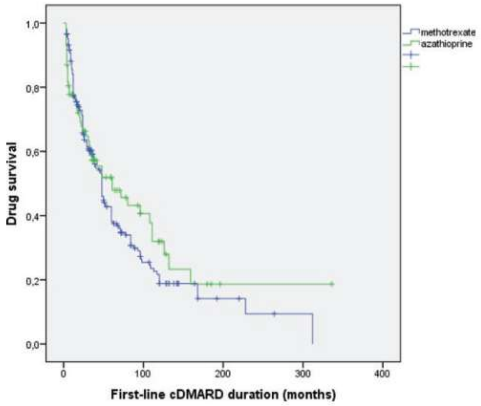
POS0219

COMPARISON OF METHOTREXATE AND AZATHIOPRINE AS THE FIRST STEROID-SPARING IMMUNOSUPPRESSIVE AGENT IN PATIENTS WITH TAKAYASU'S ARTERITIS

S. Kaymaz Tahra[1], O. Bayindir[2], B. Ince[3], O. Ozdemir Isik[4], M. E. Kutu[5], Ö. Karakaş[6], T. Demirci Yildirim[7], Z. Ademoğlu[8], E. Durak Ediboglu[9], B. C. Uludogan[10], C. Ilgin[11], N. S. Yasar Bilge[10], T. Kaşifoğlu[10], S. Akar[9], H. Emmungil[8], F. Onen[7], A. Omma[6], N. A. Kanıtez[12], A. Yazici[4], A. Cefle[4], M. Inanc[3], K. Aksu[2], G. Keser[2], H. Direskeneli[13], F. Alibaz-Oner[13].

	Total group (n=301)	First-line methotrexate (n=204)	First-line azathioprine (n=77)	p
Age, mean±SD	42,2±13,3	43,5±13,3	40,4±13,2	0,08
Gender, female, n(%)	260 (86)	184 (90)	63 (82)	0,055
Duration of first cDMARD, months	35 (3-336)	35,5 (3-312)	35 (3-336)	0,64
Remission with first cDMARD, n(%)	193/296 (65)	138/199 (69)	50/77 (65)	0,48
Vascular surgery rate with first cDMARD, n(%)	40/291 (14)	17/196 (9)	18/77 (23)	**0,001**
GC dose reduction (≤5 mg) or discontinuation with first cDMARD, n(%)	153/220 (70)	110/145 (76)	100/65 (62)	**0,034**
Radiographic progression, n(%)	75/142	48/98	22/39	0,43

Drug Survival

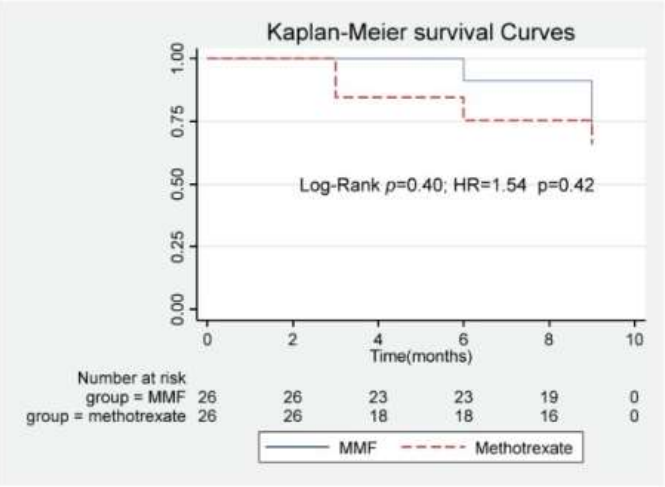


Clinical and angiographic outcomes of mycophenolate versus methotrexate in South Asian patients of Takayasu arteritis: Results from an open-label, outcome-assessor blinded randomized controlled trial

Shivraj Padiyar[a,†], Debashish Danda[a,*,†], Ruchika Goel[a], Elizabeth Joseph[b], Aswin M. Nair[a,‡], George Joseph[c] and Belavendra Antonisamy[d]

Modern Rheumatology, **34**, 2024, 175–181

Outcome/response	MMF ($n=21$)	Methotrexate ($n=22$)
Per-protocol analysis		
Primary outcome		
Clinical responders, *n* (%)	15 (71.4)	14 (63.6)
Secondary outcomes		
Delta ITAS[a]	3.48 (3.2)	2.18 (3.8)
Delta ITAS CRP[a]	3.85 (3.7)	2.95 (4.0)
Time to the first failure, months[b]	9 (3–9)	4.5 (3–9)
Angiographic response, *n* (%)		
Improved	3 (15)	5 (25)
Stable	14 (75.0)	12 (60)
Worsened	3 (15)	3 (15)

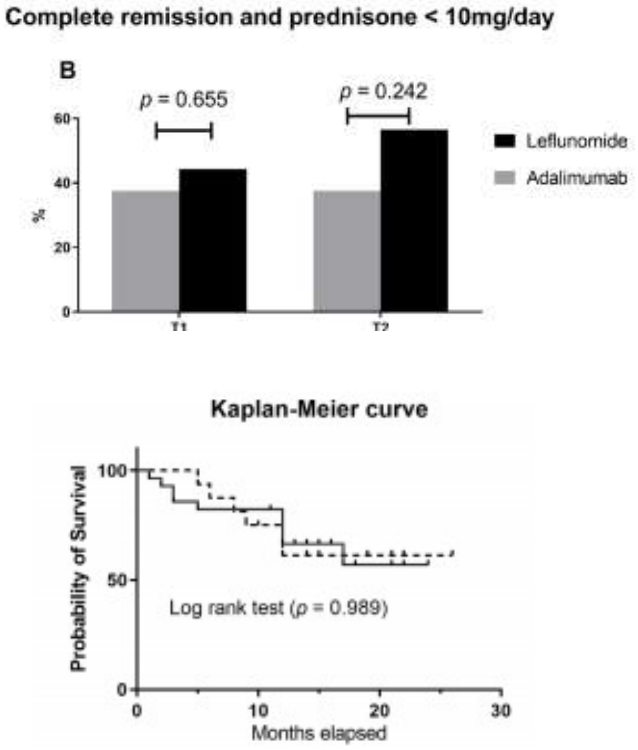


Leflunomide has a similar efficacy to Adalimumab in TAK

- 15 month follow-up
- Leflunomide patients are older with longer disease duration

Variables	ADA (n=16)	LEF (n=28)	P value
Demographics			
Age at baseline, years	35.0 (22.5–41.8)	40.5 (32.0–48.8)	0.063
Females, n (%)	15 (93.8)	25 (89.3)	1.000
Disease duration, months	51.0 (15.0–114.0)	108.0 (27.0–240.0)	0.183
ESR, mm/hour	21.0 (6.8–35.3)	20.5 (10.3–32.0)	0.964
Elevated ESR at baseline*, n (%)	7 (50.0)	12 (50.0)	1.000
CRP, mg/L	8.6 (2.6–14.5)	6.5 (1.3–11.8)	0.540
Elevated CRP at baseline†, n (%)	6 (66.7)	12 (60.0)	1.000
Active disease at baseline according to Kerr's criteria,[34] n (%)	14 (87.5)	23 (82.1)	1.000

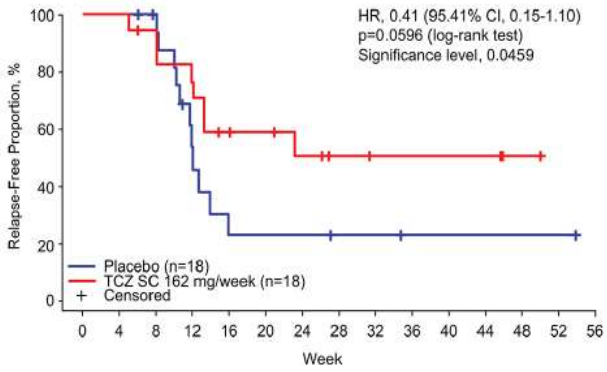
(Peron Filho F, RMD, 2024)

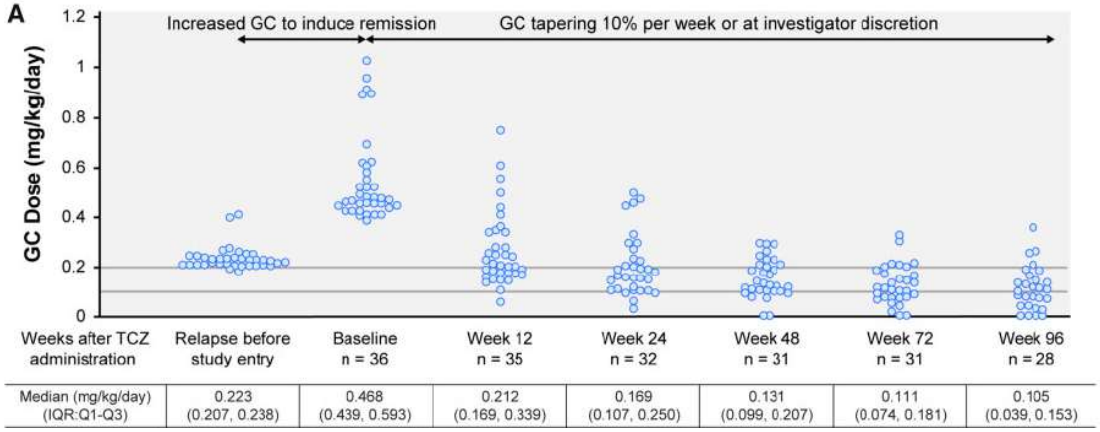


RHEUMATOLOGY

Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study

Rheumatology 2020;59:2427–2434





(Nakaoka T, Ann Rheum Dis, 2018)

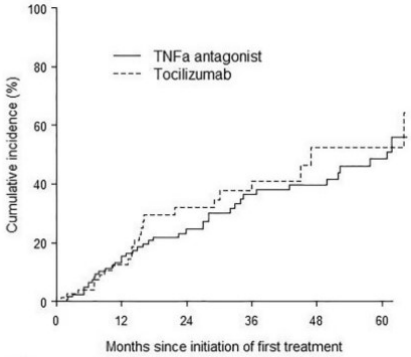
- In imaging, lesions improved in 18 % and stayed stable in 68 % (24/28)

Efficacy and safety of TNF-α antagonists and tocilizumab in Takayasu arteritis: multicentre retrospective study of 209 patients

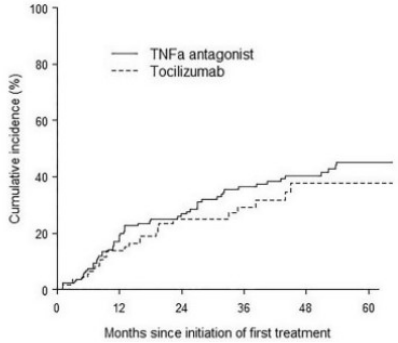
(Mekinian A, Rheumatology, 2021)

- **A retrospective multicentre study from France, Italy, Spain, Israel, Japan, Tunisia and Russia**

First Relapse



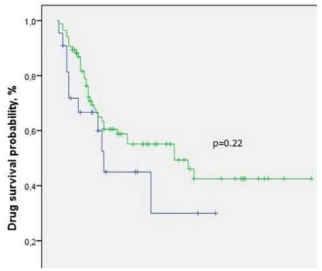
Drug Discontinuation



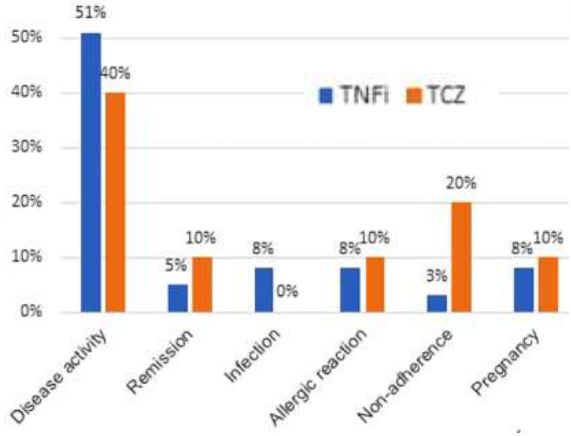
Biologic treatments in Takayasu's Arteritis: A comparative study of tumor necrosis factor inhibitors and tocilizumab

(Alibaz-Öner F, Sem Arthr Rheum, 2021)

- **111 patients, 10 Centers from Turkey**



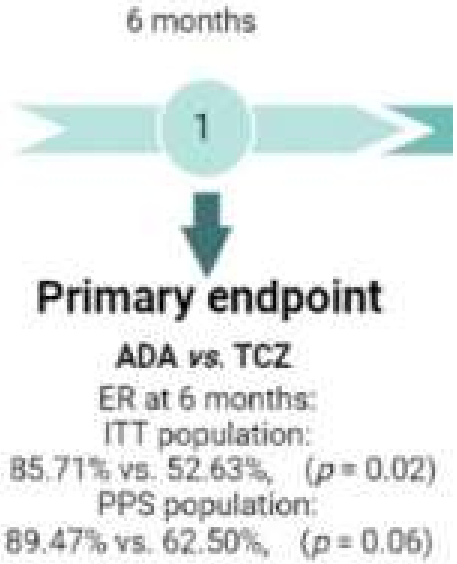
Causes for drug discontinuation

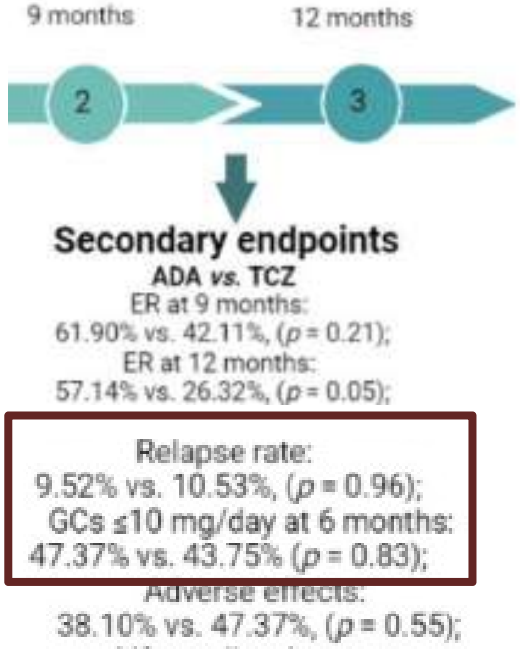


RHEUMATOLOGY

Treatment efficacy and safety of adalimumab versus tocilizumab in patients with active and severe Takayasu arteritis: an open-label study

(Wang J, Rheumatology, 2023)

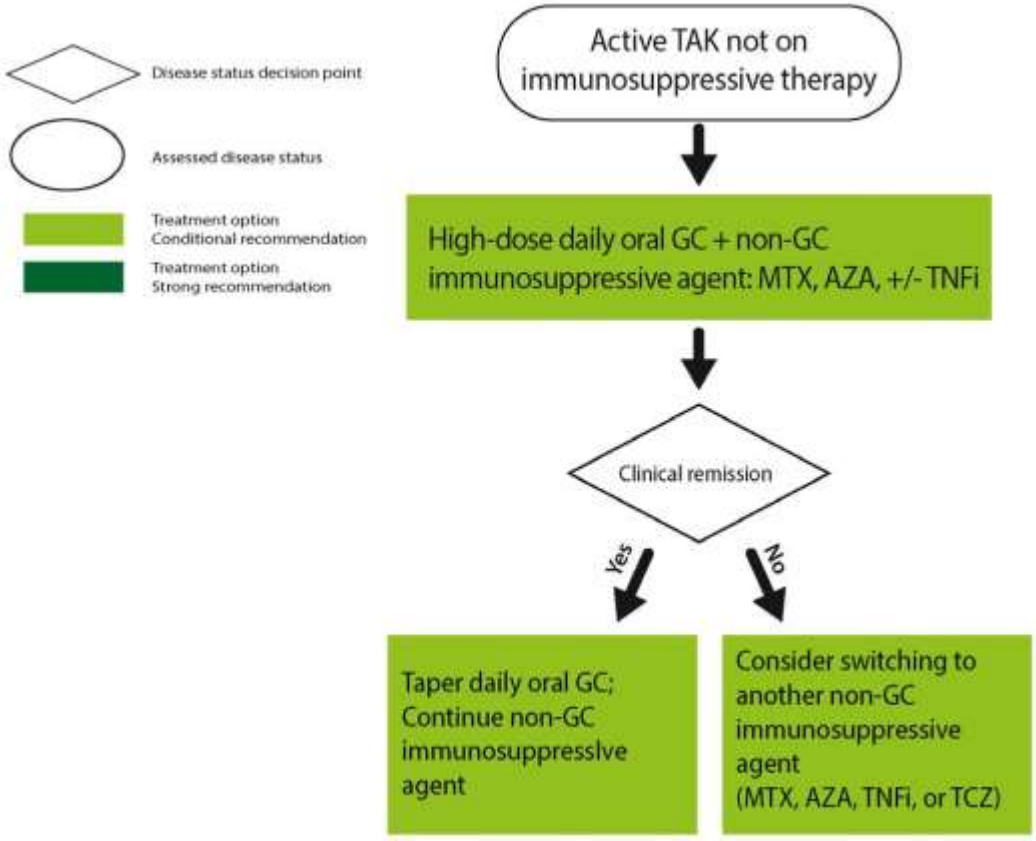




Efficacy: GC < 15 mg/day (6. month)
- or < 10 mg/day (9 and 12 m.)
- without new/worsening systemic/vascular symptoms or worsening vascular lesions in imaging

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis

(Maz M, Arthritis Rheumatol, 2021)



Why TNF Inhibitors is recommended over Tocilizumab as the initial therapy by ACR ?

- **Primary efficacy end point is not achieved in the only randomized controlled trial of Tocilizumab in TAK**
  - ***The study can be underpowered (36 patient)***

- **There is more clinical experience with and data on TNF inhibitors in TAK compared to Tocilizumab**

- **Tocilizumab use affects acute-phase reactants which may impact ability to follow disease activity**

(Maz M, Arth Rheum, 2021)

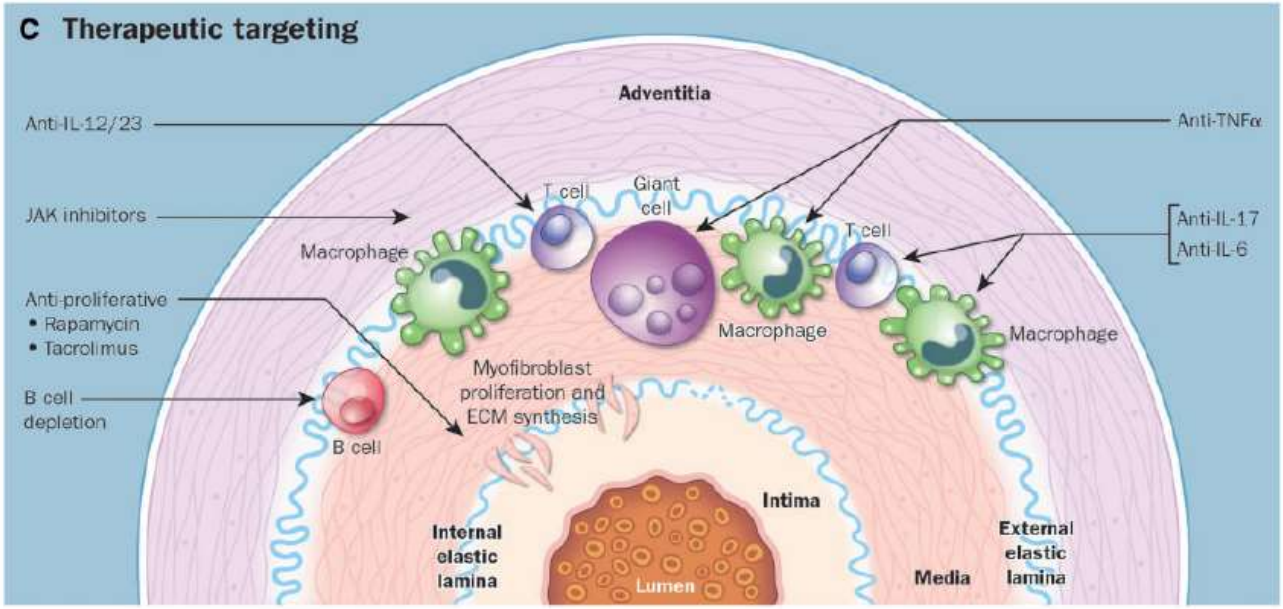
TAK patients switched to biologics has earlier onset and higher APR but no difference in disease activity at onset

Follow-up duration: 73 months in both groups

	csDMARD (n=216)	bDMARD (n=113)	p
Age	46.2±13.2	36.8±11.3	<0.01
Age at diagnosis	38.0±13.1	27.9±8.6	<0.01
Constitutional symptoms, n(%)	143 (66)	96 (85)	<0.01
Claudication, n (%)	156 (72)	71 (63)	0.08
Carotidynia, n (%)	47 (22)	31 (27)	0.28
Angiographic type 5, n(%)	84 (45)	49 (45)	0.99
ITAS 2010	11.6±4.6	11.3±6.3	0.39
CRP, baseline, mg/L	12.5 (0.2-286)	19 (0.3-280)	0.002
Number of relapses	0 (0-3)	1 (0-5)	<0.01

(Kaymaz-Tahra S, Vasculitis2024, abst)

Novel Therapeutic Targets in TAK

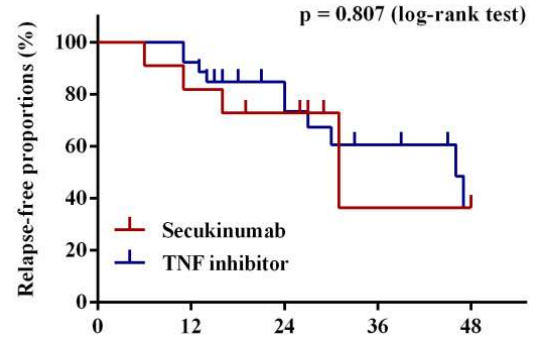


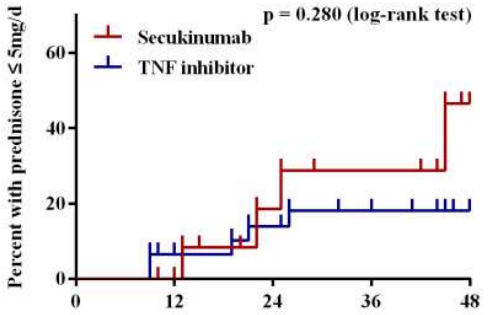
(Tombetti E, Mason JC. Rheumatology, 2019)

Secukinumab vs TNF Inhibitors

Intention-to-treat analysis	12 weeks		P-value
	Secukinumab (n=19)	TNF inhibitor (n=34)	
Overall response	6 (31.6%)	20 (58.8%)	0.057
Complete response	6 (31.6%)	18 (52.9%)	0.134
Partial response	0 (0%)	2 (5.9%)	-

Intention-to-treat analysis	24 weeks		P-value
	Secukinumab (n=19)	TNF inhibitor (n=34)	
Overall response	10 (52.6%)	22 (64.7%)	0.389
Complete response	9 (47.3%)	19 (55.9%)	0.552
Partial response	1 (5.3%)	3 (8.8%)	1.0



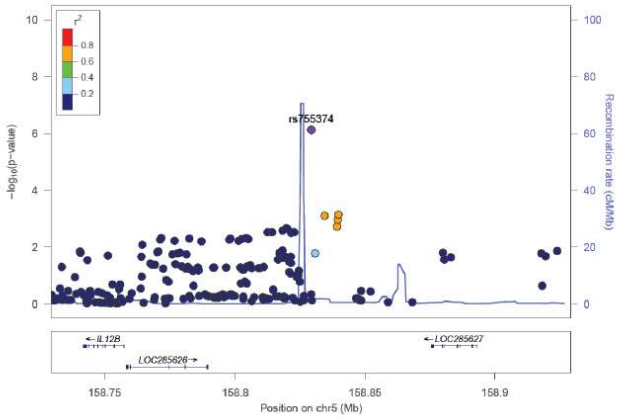


(Tian X, Arth Rheum, 2023)

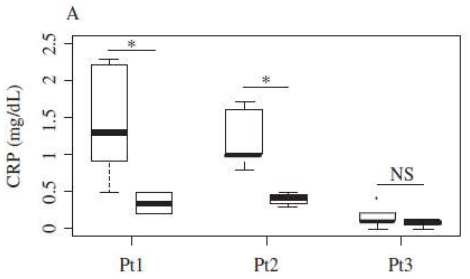
IL-12B is a common risk factor for large-vessel vasculitis

Can anti-12/23 treatments be an option in TAK ?

- **6 GCA and 2 Takayasu Cohorts**
- **IL-12B gene (rs755374):**
  - **OR: GCA: 1.16 - TAK: 1.50**



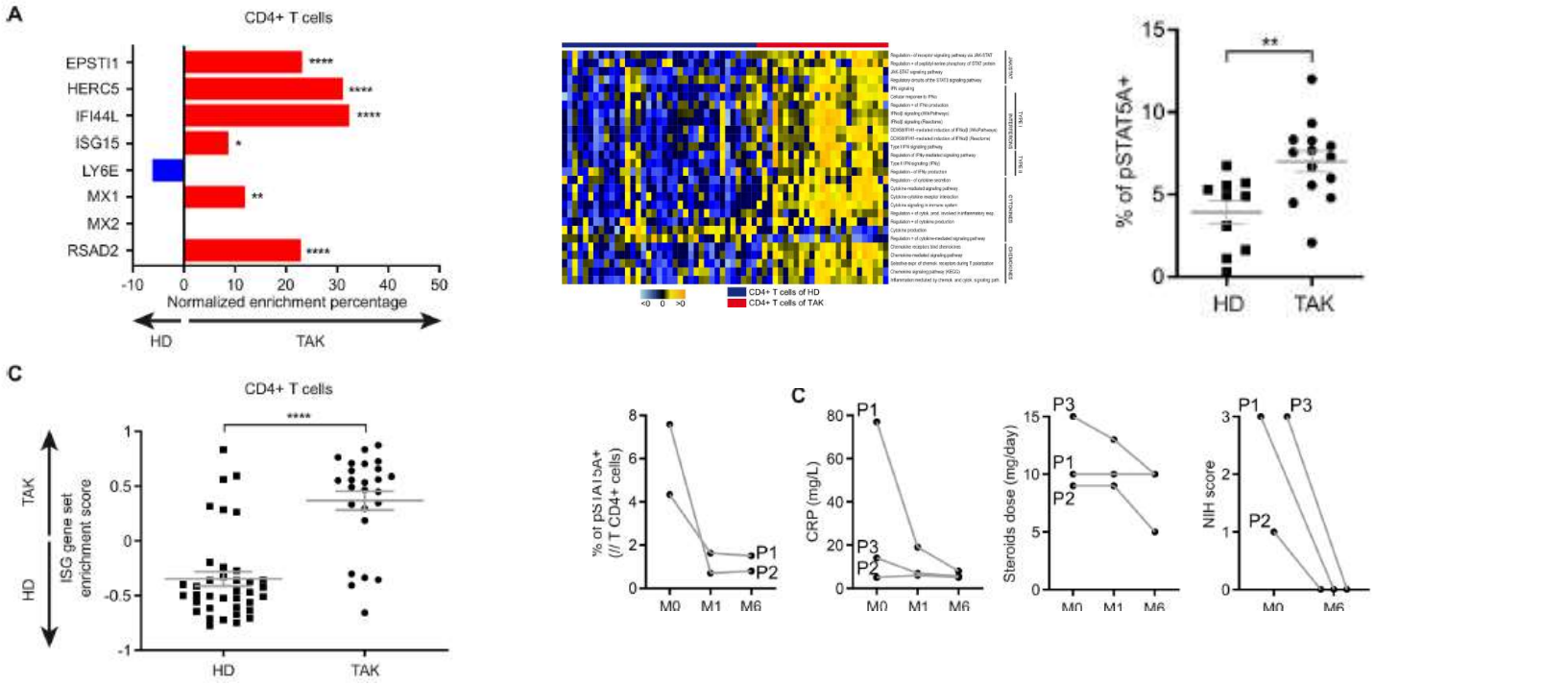
(Carmona D, Sci Rep, 2017)



VAS in Pt3		
Symptoms	Before	After
Headache	6.2	1.6±2
Neck pain	7.6	4.1±3.8
General fatigue	6.2	1.4±1.6
Muscle pain	0.5	1±1

(Terao C, Scan J Rheumatol, 2016)

Targeting JAK/STAT pathway in Takayasu's arteritis

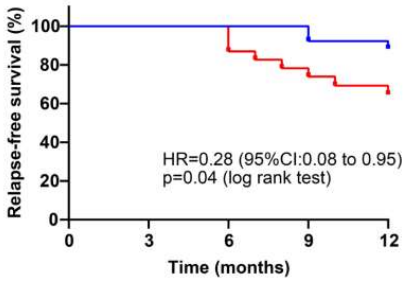


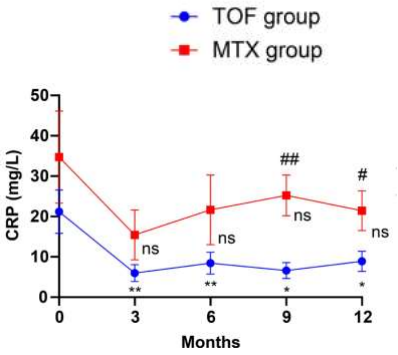
Régnier P, *et al*. *Ann Rheum Dis* 2020;

Tofacitinib is similar to Leflunomid, but better than MTX in TAK

Treatment efficacy and safety of tofacitinib versus methotrexate in Takayasu arteritis: a prospective observational study

- 53 patients

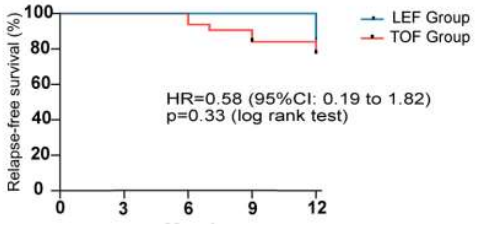


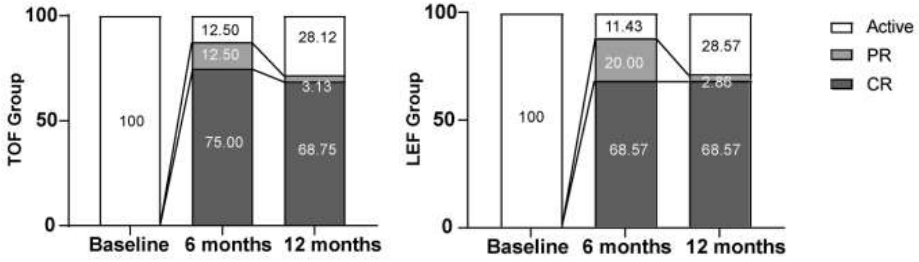


Kong X, *et al*. *Ann Rheum Dis* 2021;**0**:1–7.

Efficacy and safety of tofacitinib versus leflunomide with glucocorticoids treatment in Takayasu arteritis: A prospective study

- 67 patients



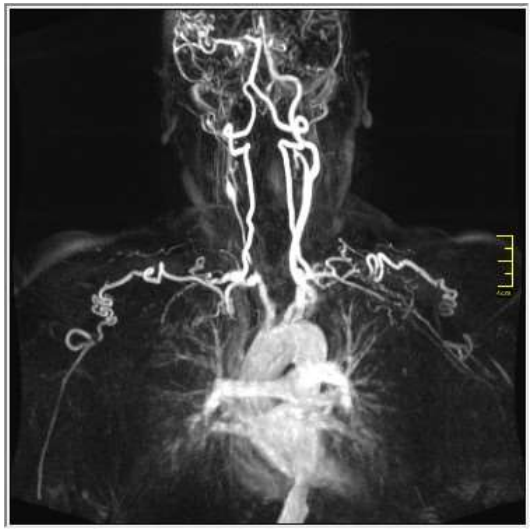


Seminars in Arthritis and Rheumatism 55 (2022) 152018

Vascular Interventions in TAK ?

When is it necessary ?

- **41 years old female**
- **15 years of symptoms**
- **Stable claudication in both arms**
  - ***Do not change with biologics***



- Extremity gangrene: 10 cases

(Misra DP, Rheumatol Int, 2016)

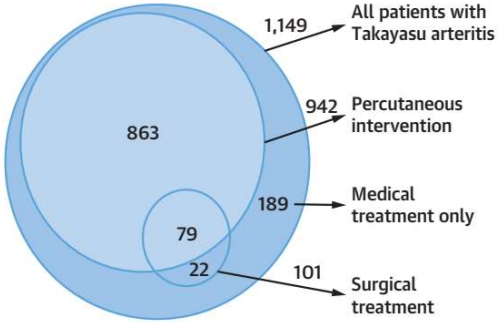
- Gastro-intestinal gangrene: 13 cases

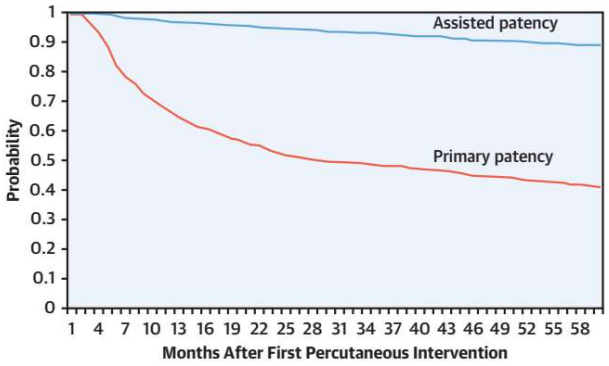
(Misra DP, Rheumatol Int, 2017)

- Recommendation: In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, we <u>conditionally recommend *against* surgical intervention</u>

(Maz M, Arthritis Rheumatol, 2021)

Outcomes of Percutaneous Intervention in Patients With Takayasu Arteritis





	Analyzable Lesions Remaining F = 2,365[b] - ΣE	Successful Follow-Up Outcome G		Cumulative Success[c] ΣG		Restenosis H	
PI	n	n	G/D%	n	ΣG/F%	n	H/D%
PI-1	1,923	935	50.3	935	48.6	907	48.8
PI-2	1,748	314	49.4	1,249	71.5	318	50.0
PI-3	1,695	82	36.8	1,331	78.5	142	63.7
PI-4	1,679	41	38.0	1,372	81.7	67	62.0
PI-5	1,669	18	42.9	1,390	83.3	28	60.9

(Joseph G, JACC, 2023)

Upper Extremity Function is impaired in TAK

- Occlusion: Left subclavian (+) : 63 % - Right subclavian (+): 55 %

	TAK (n=51)	HC (n=51)	P
UULEX (seconds)	171 ± 103	432 ± 45	0.000
R. handgrip strength (kg)	23 ± 7	27 ± 23	0.002
L. handgrip strength (kg)	22 ± 7	26 ± 8	0.014

- Active vs inactive: 104.4 vs 183.5 seconds (p=0.023)
- UULEX time associated with age, left subclavian involvement, fatigue and damage (TADS score)
- *No association with disease duration and GC dose*

UULEX
Unsupported Upper Limb Exercise Test

(Temiz F, unpublished)

Upper Extremity Function stays stable during follow-up

in patients with remission and no radiological progression

	Mean+SD	p
UULEX Initial	138 ± 67	0,046
Follow-up	178 ± 109	
RH Initial	23 ± 7	0,698
Follow-up	23 ± 6	
LH Initial	22 ± 6	0,201
Follow-up	21 ± 6	

Change	UULEX time	p
Disease Activity		
Present (n=7)	- 38 ± 63	0,001
Absent (n=17)	73 ± 87	
Radiol. Progression		
Present (n=4)	- 51 ± 93	0,081
Absent (n=20)	50 ± 73	

N=24, follow-up: mean 15.3 months

(Temiz F, unpublished)

Vascular Interventions in TAK: whom to intervene ?

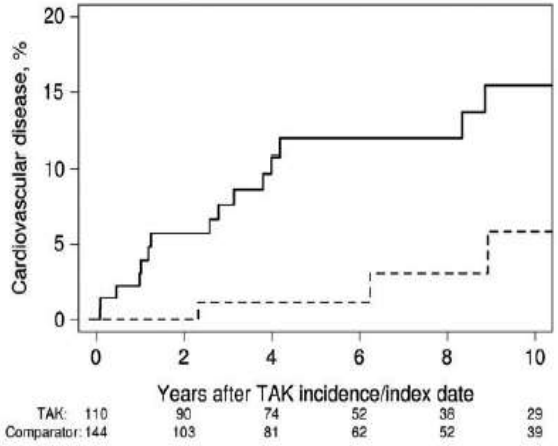
- **Uncontrolled hypertension secondary to renal artery stenosis**
- **Aortic regurtation/coarctation and aneursym repair**
- **Symptomatic cerebrovascular disease**
- **Ischemic heart disease**

(Mason JC, Current Opin Rheum, 2015)

Cardiovascular events are increased in TAK

- A combined series from Mayo Clinic, USA and Marmara University, Turkey

FIG. 1 Cumulative incidence of cardiovascular events among patients with Takayasu's arteritis and comparators



(Alibaz-Oner F, Rheumatology, 2017)

TABLE 3 Multivariable analysis for cardiovascular disease in Takayasu arteritis patients

	P	OR	95% CI
Smoking	.054	3.3	0.9-11.2
Metabolic syndrome	.007	4.9	1.5-15.6
Cumulative prednisolone	.037	1.1	1.0-1.1

(Saglam B, Int J Rheum Dis, 2022)

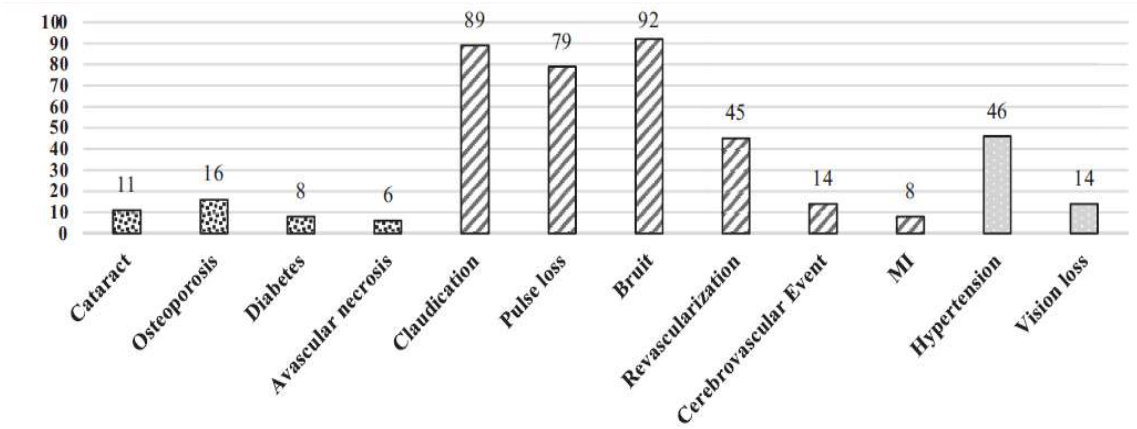
Multivariate Cox proportional hazard regression analysis estimating risk of relapse.

	Adjusted hazard ratio	95% Confidence interval	p value
Age > 40 years	0.558	0.236–1.320	0.184
Hypertension	0.720	0.301–1.721	0.459
Carotidynia	2.603	1.121–6.047	**0.026**
LDL-cholesterol	1.007	0.987–1.029	0.487
Statin use	0.260	0.120–0.563	**0.001**

(Kwon OC, Int J Cardiol, 2019)

Although relapse is frequent, damage during disease course is limited under IS therapies

- **Follow-up: mean change in VDI/TADS damage-scores: 1 (during 6.4 years)**
- **Relapses (43 %) are not associated with damage**
- **Biologic use mainly in:**
    - **Relapsing disease (29 % vs 8 %, p=0.004)**



(n=114, follow-up: 77 months)

(Kaymaz-Tahra S, Seminars AR, 2020)

Summary - Assessment in Takayasu Arteritis

- **Takayasu's arteritis has a chronic course with remission and relapses**
  - ***Damage is limited in early-onset disease***

- **MRI is usually sufficient to diagnose TAK**
  - ***Convenional angiography is not recommended***

- **New 'cluster analysis' might be useful to predict prognosis**

- **Relapses are frequent during follow-up, but whether relapses are associated with cumulative damage is not clear**
  - ***In retrospective assessment most damage is already present in diagnosis***

Summary - Management of Takayasu Arteritis

- **Management requires a multi-disciplinary approach**

- **Immunosuppressives +/- biological treatments are effective in most patients**
  - ***Mycophenolate and Leflunomide seem to be better as CISs***
  - ***TNF-inhibitors as the first choice biologic agent ?***
  - ***JAK-inhibitors seem to be promising***

- **However, long-term prognosis in TAK is still unsatisfactory with:**
  - ***Increased vascular stenosis/aneurysms with late diagnosis***
  - ***Glucocorticoid-associated damage***
  - ***Cardiovascular events***

RHEUMATOLOGY SOCIETY OF TURKEY

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