

Vasculitis: Pearls for early diagnosis and treatment of Giant Cell Arteritis

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I have no relevant financial relationships or affiliations with commercial interests to disclose.

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I will be discussing experimental or off-label drugs, therapies and/or devices that have not been approved by the FDA.

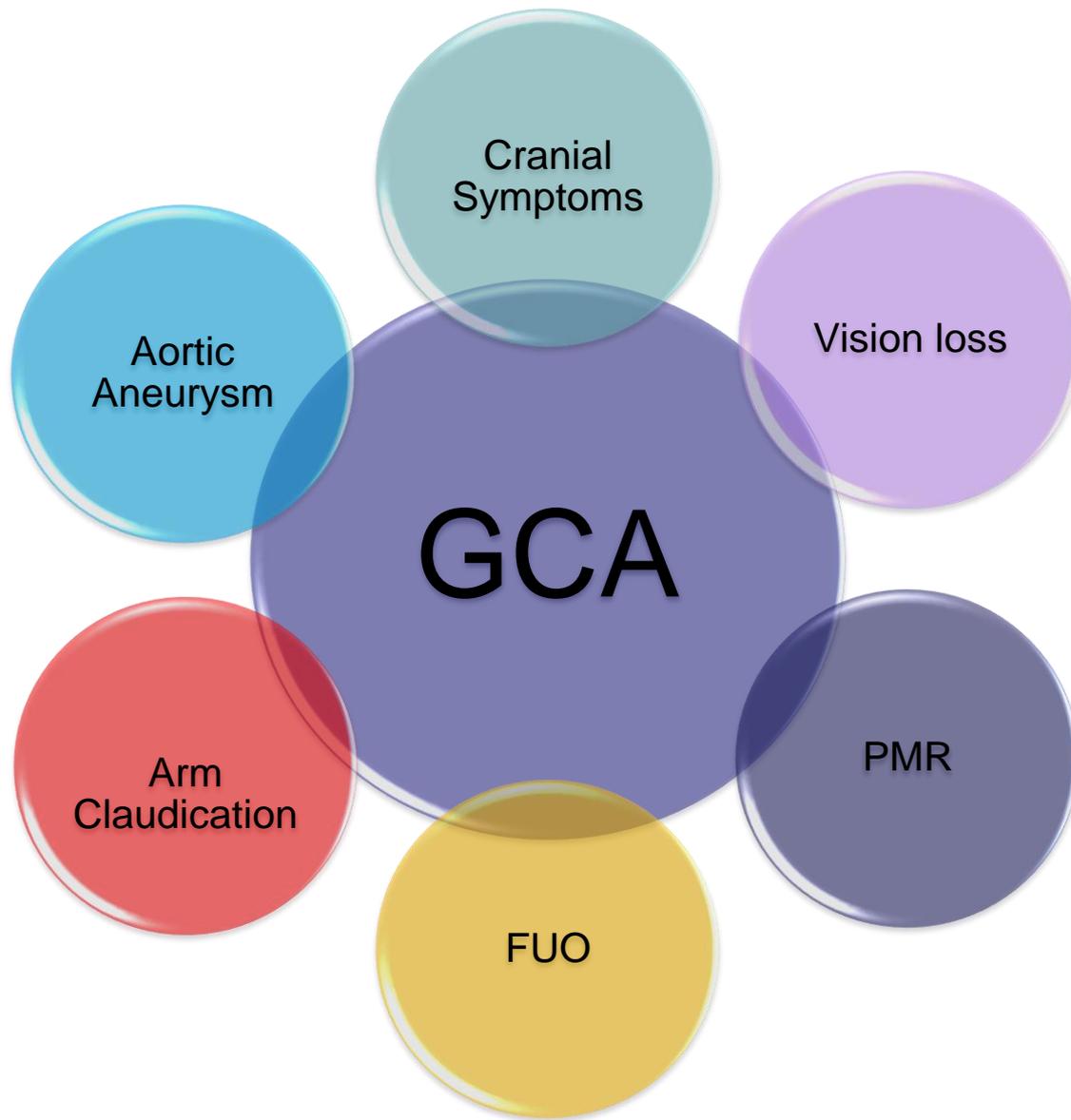
Objectives

- To recognize early signs of vasculitis.
- To discuss Tocilizumab (IL-6 inhibitor) as a new treatment option for temporal arteritis.
- To recognize complications of vasculitis and therapies.

Professional Practice Gap

Gap 1: Application of imaging recommendations in large vessel vasculitis

Gap 2: Application of tocilizimab in treatment of giant cell vasculitis



Which is not a risk factor or temporal arteritis?

- A. Smoking
- B. Female sex
- C. Diabetes
- D. Northern European ancestry
- E. Age

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Giant Cell Arteritis

- Most common form of systemic vasculitis in adults
 - Incidence: ~ 1/5,000 persons > 50 yrs/year
 - Lifetime risk: 1.0% (F) 0.5% (M)
- Cause: unknown

At risk:

Women (80%) > men (20%)

Northern European ancestry >>> AA > Hispanics

Age: average age at onset ~73 years

Smoking: 6x increased risk

Biomarkers predicting biopsy proven GCA

For predicting biopsy proven GCA²

- ESR: 89% have ESR >50
 - 11% have ESR < 50 mm/h¹
 - Sens 84%²
- C-Reactive Protein
 - Sens 86%; Spec 30%; NPV 88%²
 - 4% of biopsy proven GCA had normal ESR and CRP
- Both elevated: OR 3.06 (95% CI 2.03, 4.62)²

What is not a symptom of GCA?

- A. Visual loss
- B. Arm claudication
- C. Vertebral artery stroke
- D. Hallucinations
- E. Muscle weakness

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Giant cell arteritis: Clinical presentation & labs

| Clinical Manifestation | Prevalence |
|---|------------|
| Constitutional symptoms: (including fevers/FUO) | Almost all |
| New onset headache | 76% |
| Jaw claudication: most specific | 34% |
| Vision loss: complete or partial; unilateral or bilateral | 15-20% |
| • Visual hallucinations | 20% |
| • Diplopia: highly specific | 5% |
| Polymyalgia rheumatica | 40-50% |
| Temporal artery abnormality | <50% |
| ESR \geq 50 mm | 90% |
| Increased alkaline phosphatase | ~25% |



Two ends of the same disease spectrum ?

Polymyalgia
Rheumatica



15-20% have GCA

Giant Cell
Arteritis



40-60% have PMR

Case #1

65 y/o white man with headache, visual changes and increased inflammatory markers

- 3 months of fatigue and decreased appetite without weight loss, attributed to stress
- 3 months of episodic blurry vision, affecting both eyes for the past 2 months. No visual field defect.
- New occipital and temporal headache for the past 2 weeks, with no previous history of headaches
- No fevers, scalp tenderness, shoulder/hip girdle symptoms, or jaw claudication
- Exam: Well appearing. Symmetric blood pressures in arms and legs, no carotid bruits. Temporal arteries non-tender with normal pulses
- ESR 12, CRP 72.8 (normal <8.0 mg/dL)

What should be the next step performed in his diagnostic evaluation?

- A. Biopsy the temporal artery
- B. Obtain color Doppler ultrasound of the temporal and/or axillary arteries
- C. Obtain high resolution magnetic resonance angiogram of the cranial arteries
- D. Obtain positron emission tomography with low-dose computed tomography imaging of the cranial arteries

Imaging in large vessel vasculitis: EULAR

- Recommendation 1: early imaging test is recommended to complement the clinical criteria for diagnosing GCA, assuming high expertise and prompt availability of the imaging technique. Imaging should not delay initiation of treatment.
 - In settings where imaging modalities are not readily available or expertise with imaging in GCA is questionable, a biopsy should still be favored in first place.
 - Imaging should be performed before or as early as possible after initiation of therapy, best within 1 week, because treatment with glucocorticoids rapidly reduces the sensitivity of imaging.

Additional EULAR recommendations

- Recommendation 3: Ultrasound of temporal ± axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA. A non-compressible 'halo' sign is the ultrasound finding most suggestive of GCA.
- Recommendation 4: High resolution MRI of cranial arteries to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive.

Imaging: Ultrasound

Color Doppler ultrasonography (arteries)

- Stenosis, occlusion, mural thickening
 - Stenosis of 50% or more: specificity 78-100%
 - Halo sign: specificity 100%
- Differences in interpretation
 - Variability in probe settings
- Less experienced operators
 - Does not recognize



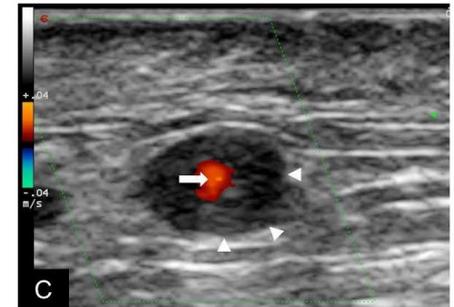
(arteries)
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78-

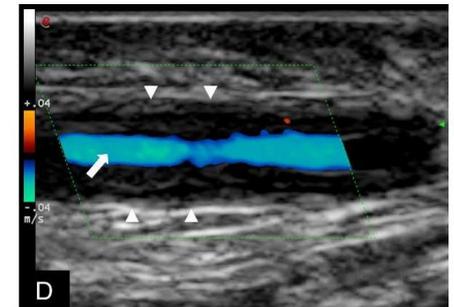


ent,

Halo Sign Transverse



Longitudinal



Imaging: Temporal Artery MR

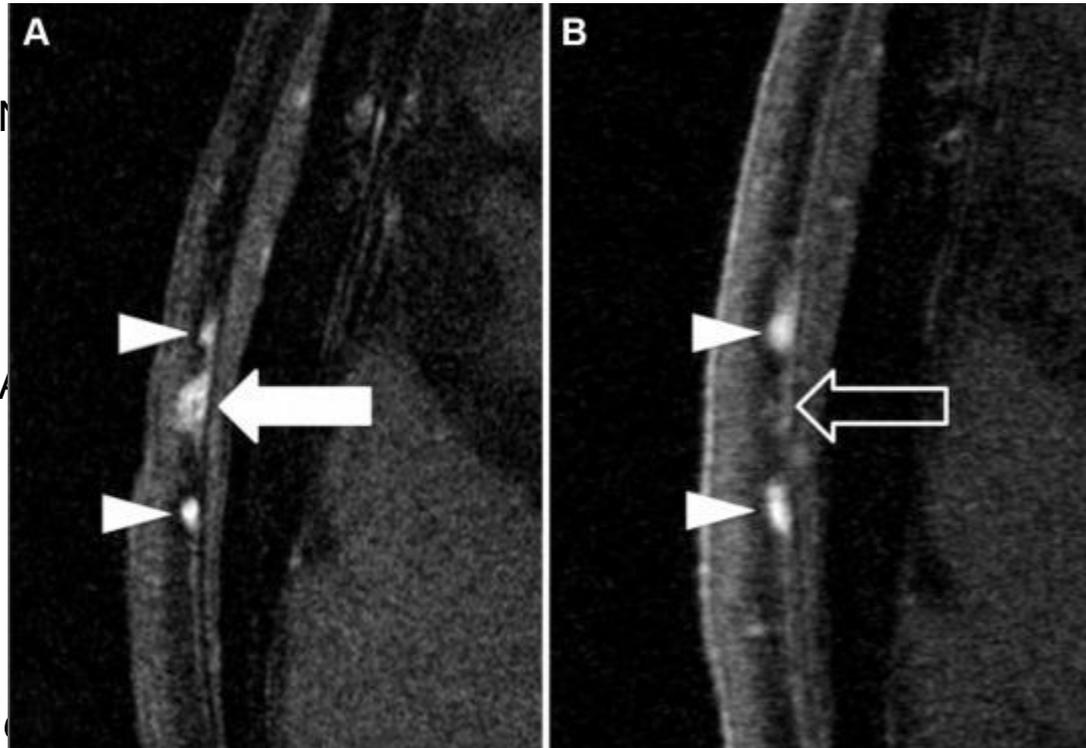
Contrast-enhanced high-resolution MRI of temporal and occipital arteries

- Arterial wall thickening with mural and periadventitial contrast enhancement
- Sensitivity 68-89%, specificity 73-97% (5 studies, n=341 total)

171 patients with suspected *GCA*: Postcontrast T1-weighted spin-echo MRI of scalp arteries (using 3T MRI) followed by temporal artery biopsy

- Positive temporal artery biopsy 18% (n=31); abnormal MRI 35% (n=60); clinical dx of *GCA* 48%
- Sensitivity 94%, specificity 78%
- Negative predictive value 98%, positive predictive value 48%

Imaging: MRA of cranial vessels



- Note:
 - Single
 - Experience and volume are critical
 - Rapid changes with prednisone—need to obtain within days of starting

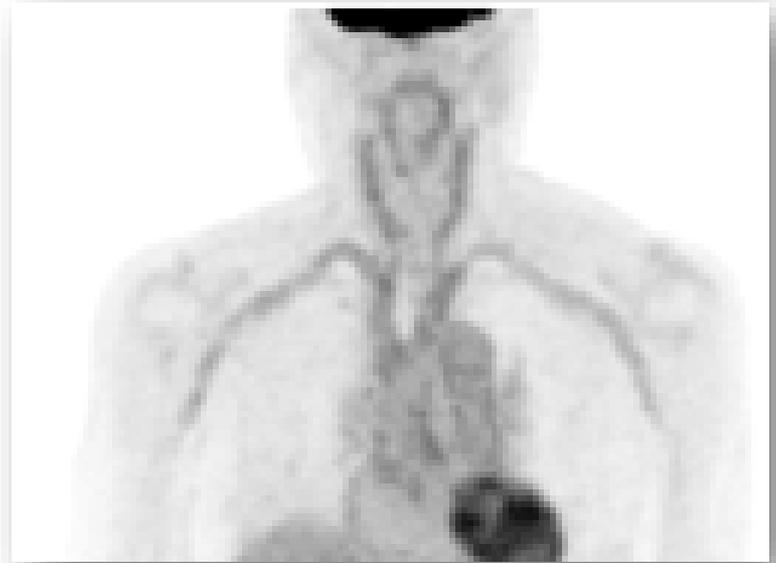
EULAR Imaging Recommendations

- Recommendation 5: CT and PET are not recommended for the assessment of inflammation of cranial arteries.
- Recommendation 6: Ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of large vessel GCA.

GCA

Upper Extremity Arterial Involvement

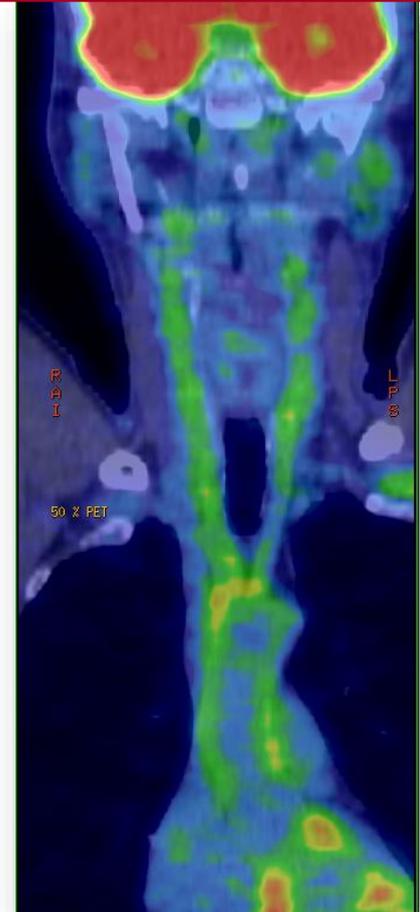
- Frequency by imaging:
 - PET CT- 74%
 - CT angio - 42%
 - Ultrasound - 30%
- Symptoms < 10%
- Isolated PMR
 - PET - 31%



Blockmans D et al. Rheumatology (Oxford) 2007; 46: 672–77
Schmidt WA et al. Rheumatology (Oxford). 2008 Jan;47(1):96-101
Ghinoi A et al. Rheumatology (Oxford). 2012 Apr;51(4):730-4
Prieto-Gonzalez S, et al. Ann Rheum Dis 2012;71:1170–6

[¹⁸F]FDG PET for GCA

- Not useful for the temporal arteries
- Useful for select cases
 - Negative TA biopsy
 - Atypical symptoms
 - FUO
- Exclude other conditions



GCA

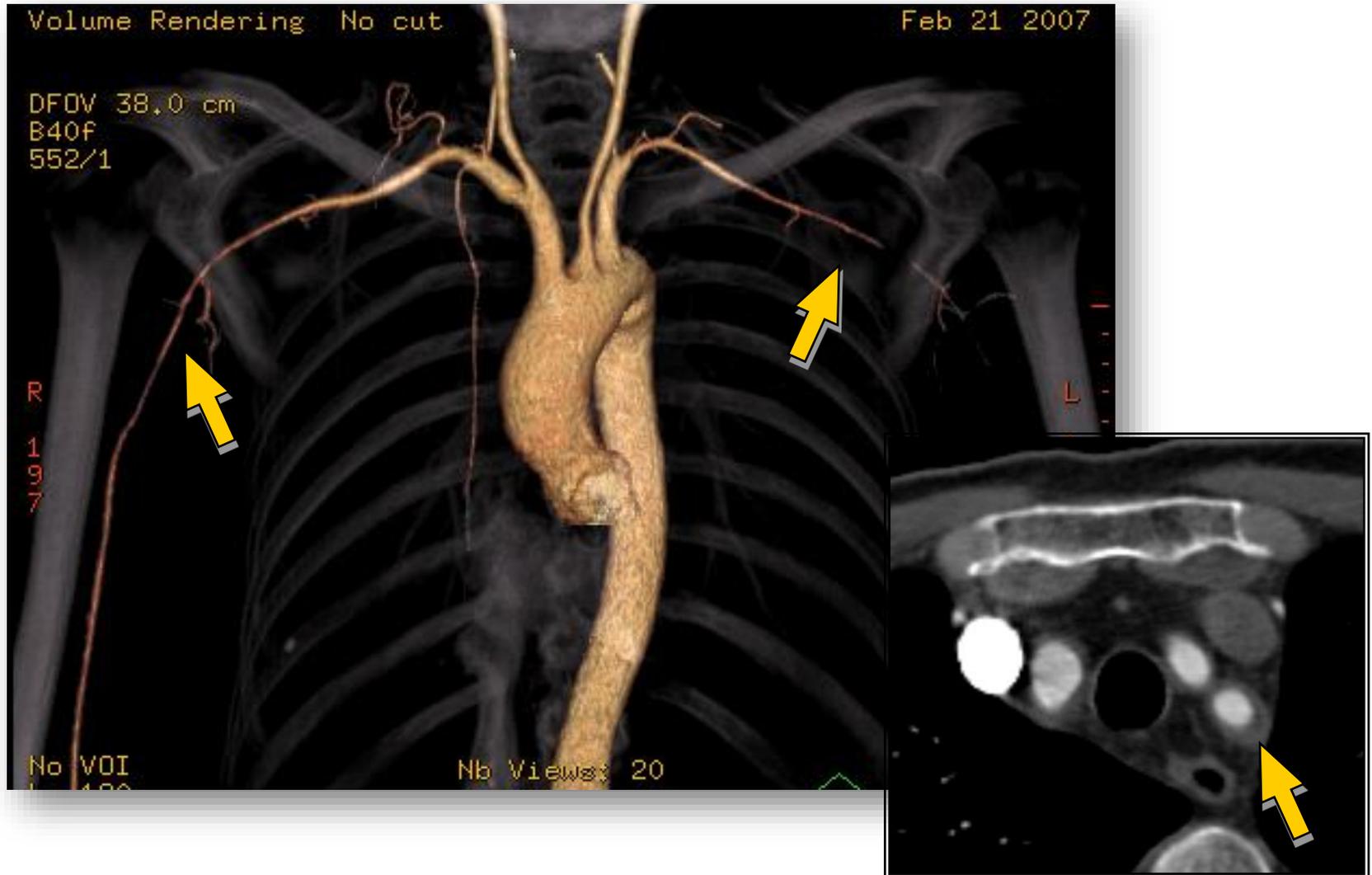
Lower Extremity Arterial Involvement

- Imaging
 - PET: 37%
 - Ultrasound: 12-50%
- Proximal arterial disease
- Clinical
 - Leg Claudication 1-20%
 - Often presenting feature
 - 15-30% critical leg ischemia



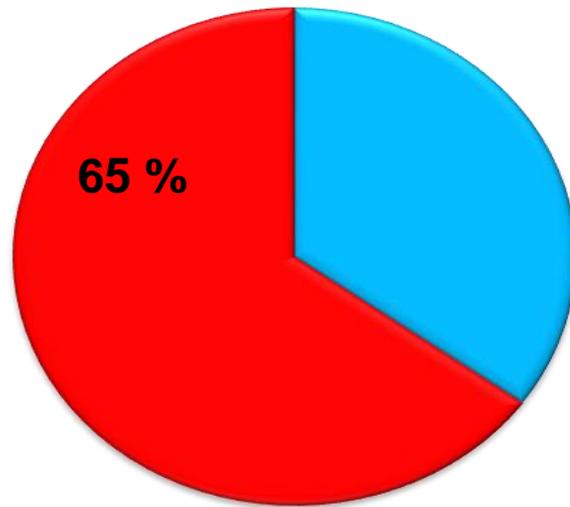
Blockmans D et al. Arthritis Rheum. 2006 Feb 15;55(1):131-7
Aschwanden M et al. Ann Rheum Dis 2010; 69:1356–1359
Czihal M et al. J Rheumatol. 2012 Feb;39(2):314-21
Kermani TA et al. J Rheumatol. 2009 Oct;36(10):2277-83

GCA - Arterial Stenosis



Aortitis is common at onset of GCA

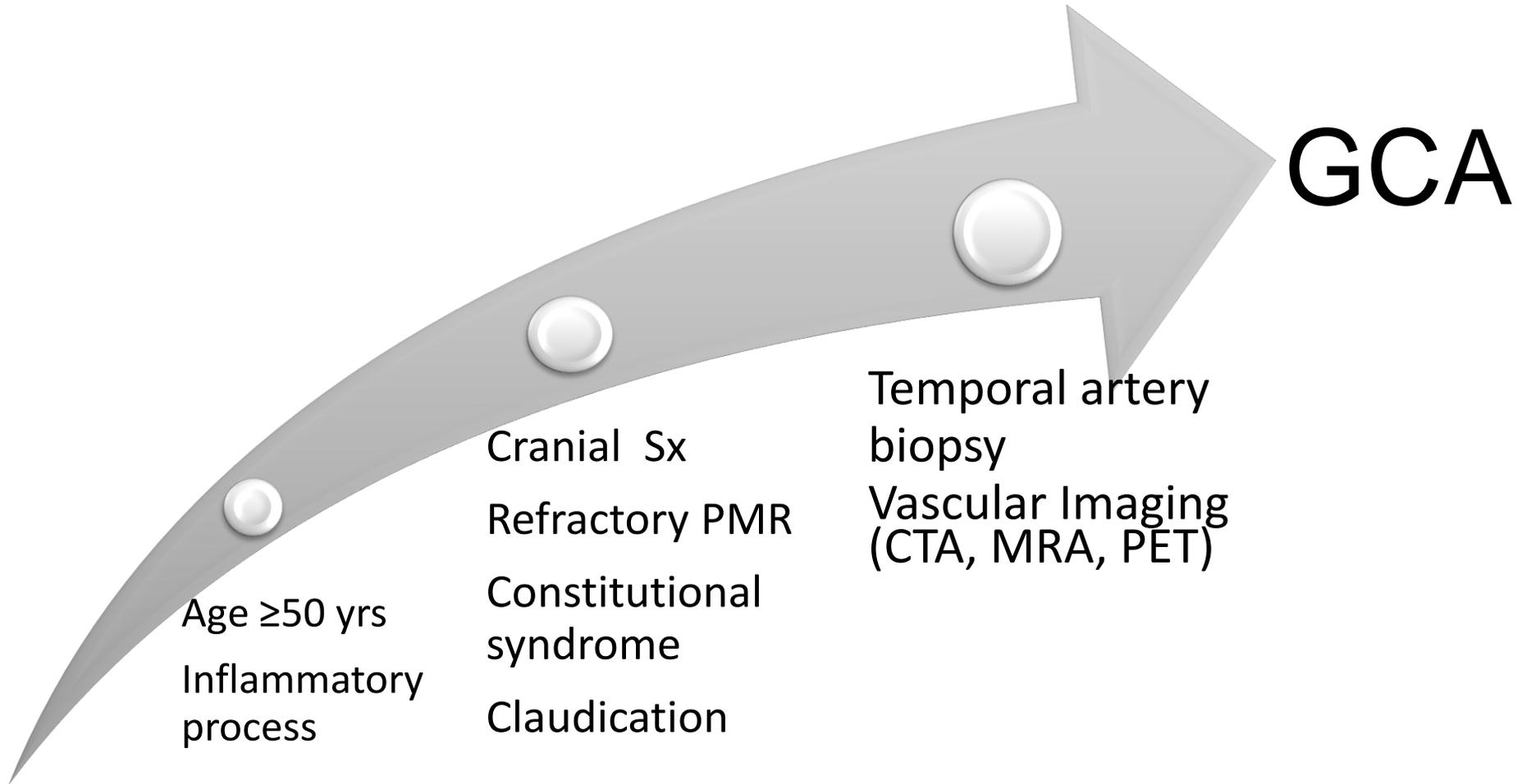
CT Angio (thickening)



- Non-involved
- Aorta inflamed



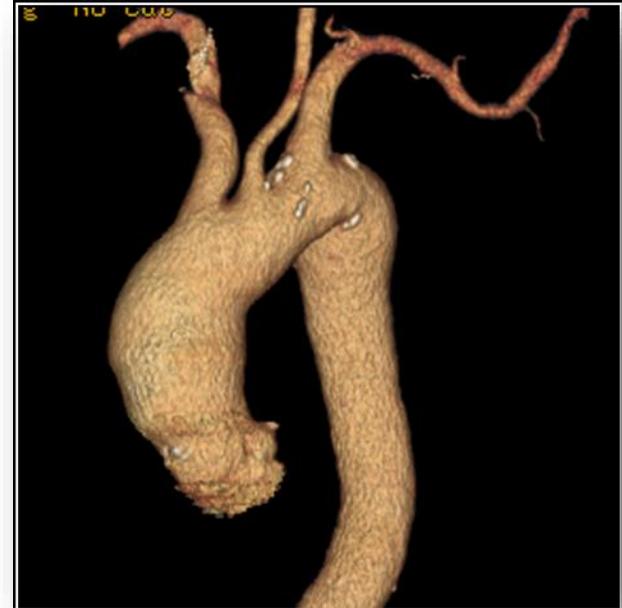
Diagnostic algorithm



GCA

Aortic Aneurysm

- Thoracic Aortic Aneurysms
 - 17.3x fold increased risk
 - **12% - 33% incidence** (10 yr F/U)
- No consistent clinical predictors
 - Aortic Regurgitation



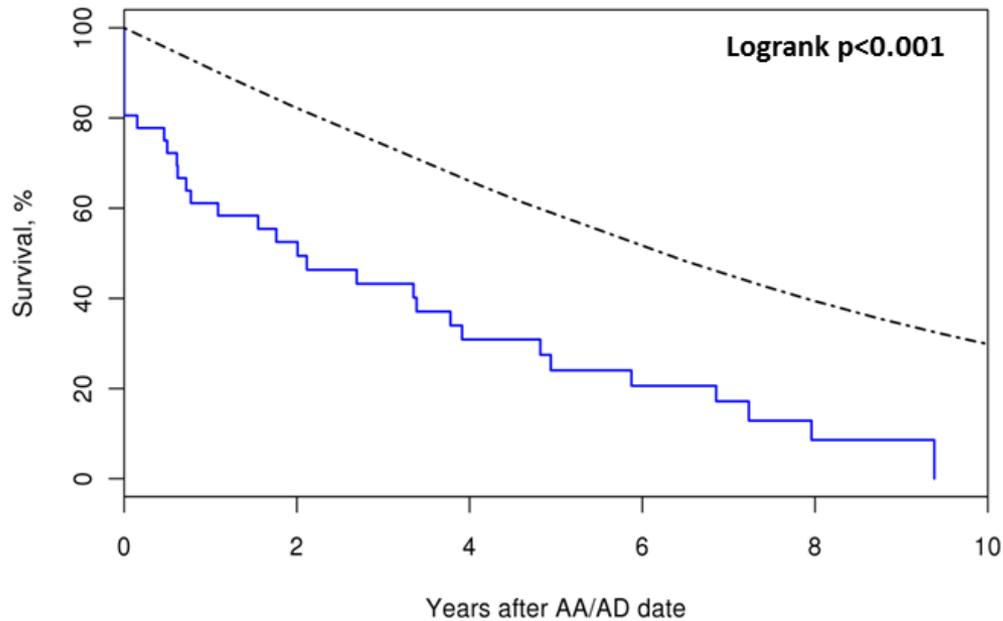
Evans JM et al. Ann Intern Med 1995;122(7):502-7

Robson JC. Ann Rheum Dis. 2013 Oct 4

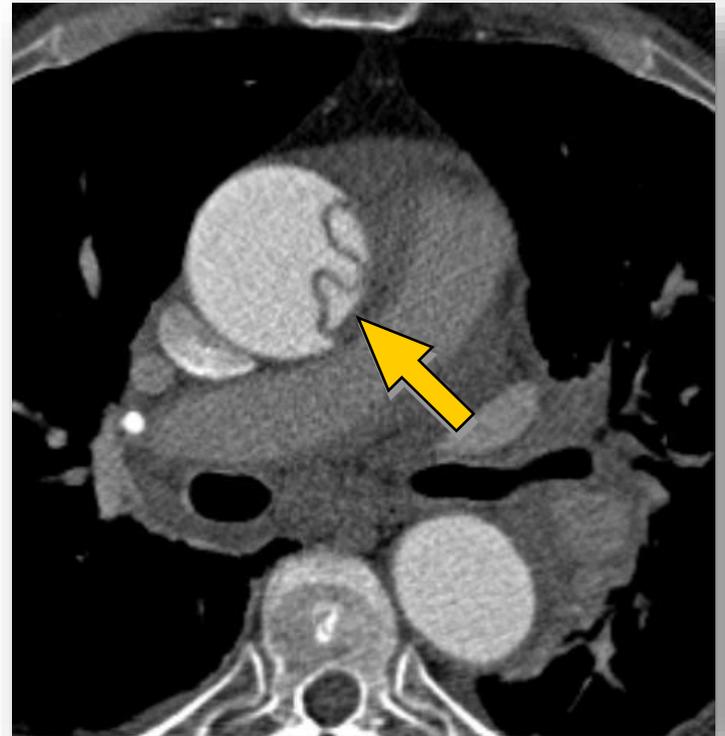
Kermani TA, Warrington KJ, et al. Ann Rheum Dis. 2012 Dec 19.

García-Martínez A, et al Ann Rheum Dis. 2013 Jul 19

Aortic aneurysm & dissection lead to increased mortality in GCA



Aneurysm/Dissection
Subjects

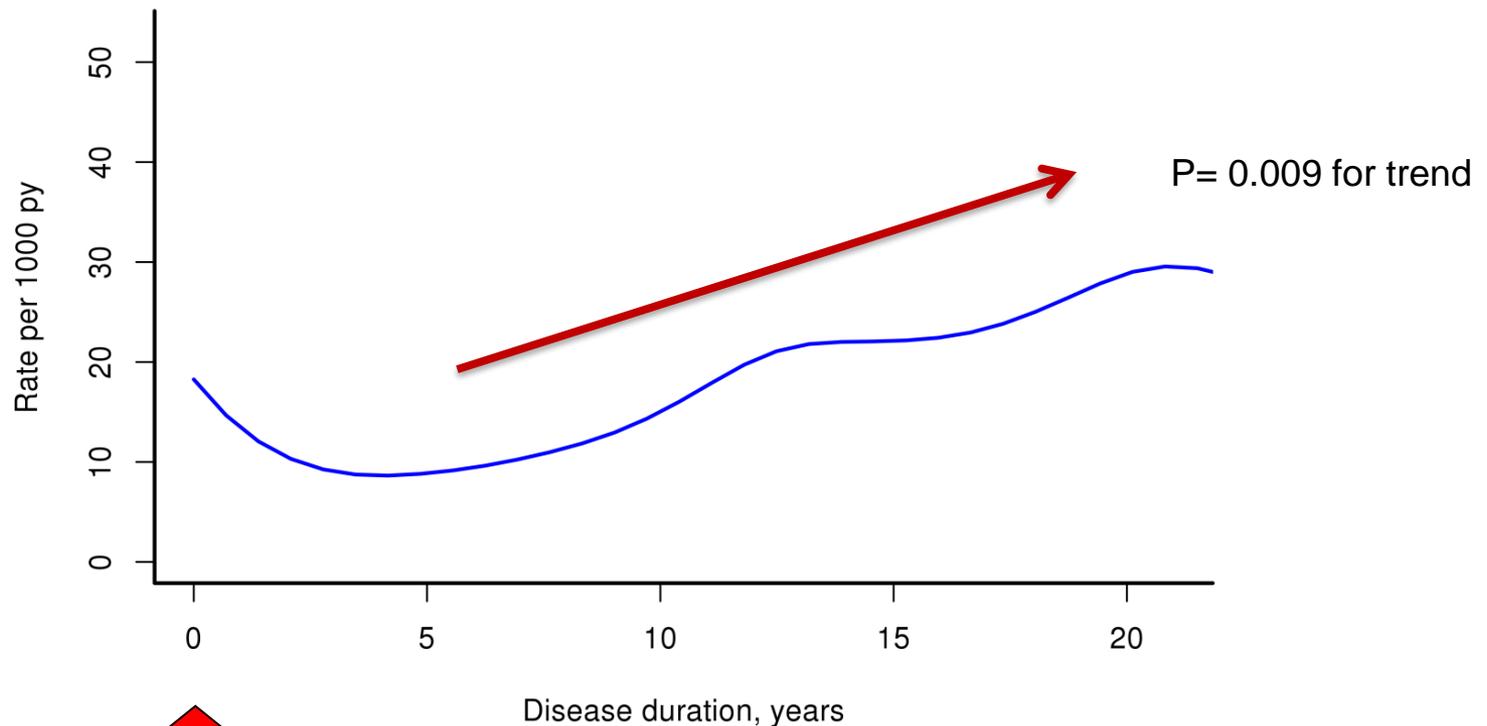


Aneurysm screening in GCA

- Expert recommendations:
 - Yearly Chest X-ray
 - Echocardiogram
- Baseline CT scan or MRI (ACC/SVM)
- To detect one previously unknown thoracic aorta aneurysm or dissection
 - 5 to 10 patients with GCA would need aortic imaging

Salvarani C et al Lancet. 2008 Jul 19;372(9634):234-45
Bongartz, Matteson. Curr Opin Rheumatol 2006;18:10–17
Mackie SL et al. Ann Rheum Dis. 2012 Dec 22
Hiratzka LF, et al. J Am Coll Cardiol 2010;55:e27–129

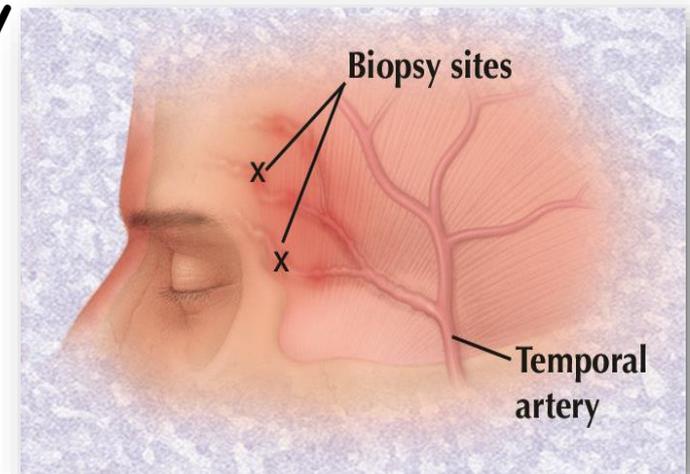
Aortic Aneurysm - Mainly a late complication when the disease is clinically in remission




GCA

Who should be referred for biopsy ?

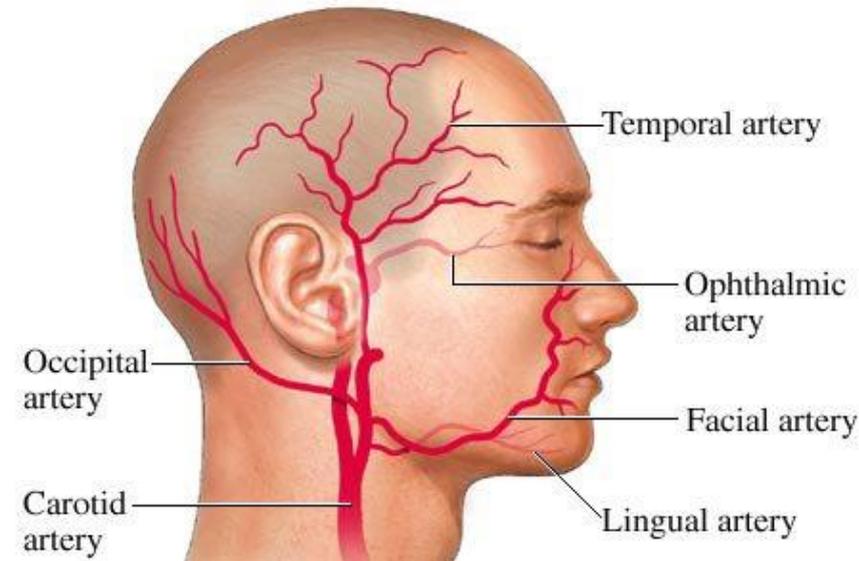
- Positive predictors
 - Jaw claudication (LR 4.2, 95% CI 2.8-6.2)
 - Diplopia (LR 3.4, 95% CI, 1.3-8.6)
- Negative predictors of +biopsy
 - Normal ESR
 - No Jaw claudication
 - No temporal artery tenderness
 - Synovitis



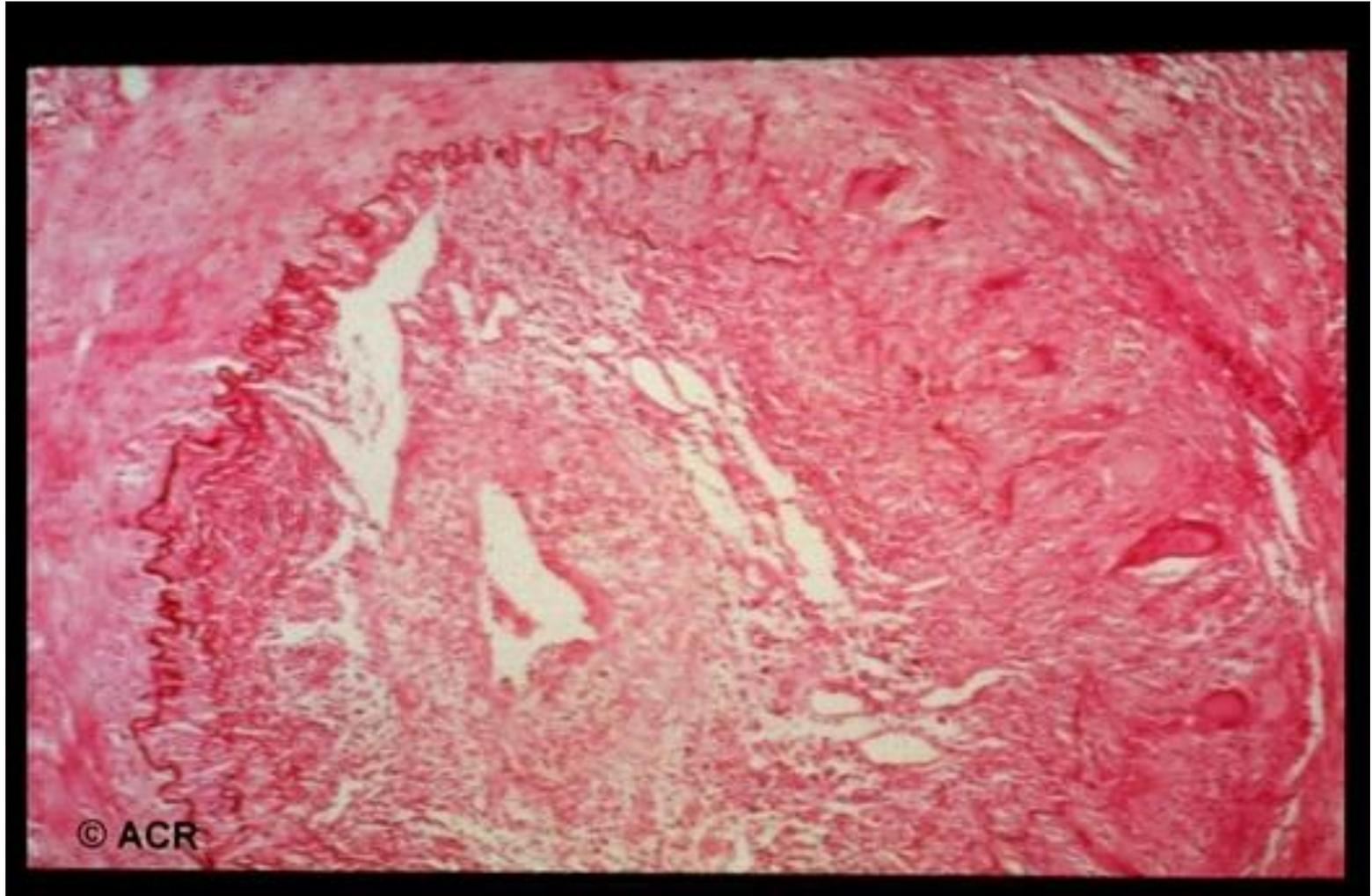
1. Rieck KL et al; J Oral Maxillofac Surg. 2011 Jan;69(1):36-40
2. Smetana GW, Shmerling RH. JAMA 2002;287(1):92-101
3. Gabriel, et al; J Rheumatology 1995; 22(1):93

GCA Complications

- Blindness
- Tongue infarction
- Scalp infarction



Histologic appearance of Giant Cell Arteritis



Diagnosis of GCA

- Temporal artery biopsies always preferred.
 - Symptomatic side, PPV 90%
 - If negative, biopsy other side (1-5%)
- Biopsy length matters! Longer is better due to skip lesions (<6mm 19% +, 6-19mm 70% +, >20mm 89%+)
- Do not withhold steroids. Biopsies will still show active or healing vasculitis for 6 weeks of steroid therapy!
- Sensitivity ~70-90%
- ~20-30% of suspected GCA pts have positive bx

GCA Treatment

72 y/o woman presents with classic symptoms of giant cell arteritis including amaurosis fugax of the left eye. Temporal artery biopsy shows transmural mononuclear cell infiltrates with multinucleated giant cells. Your initial treatment of choice is:

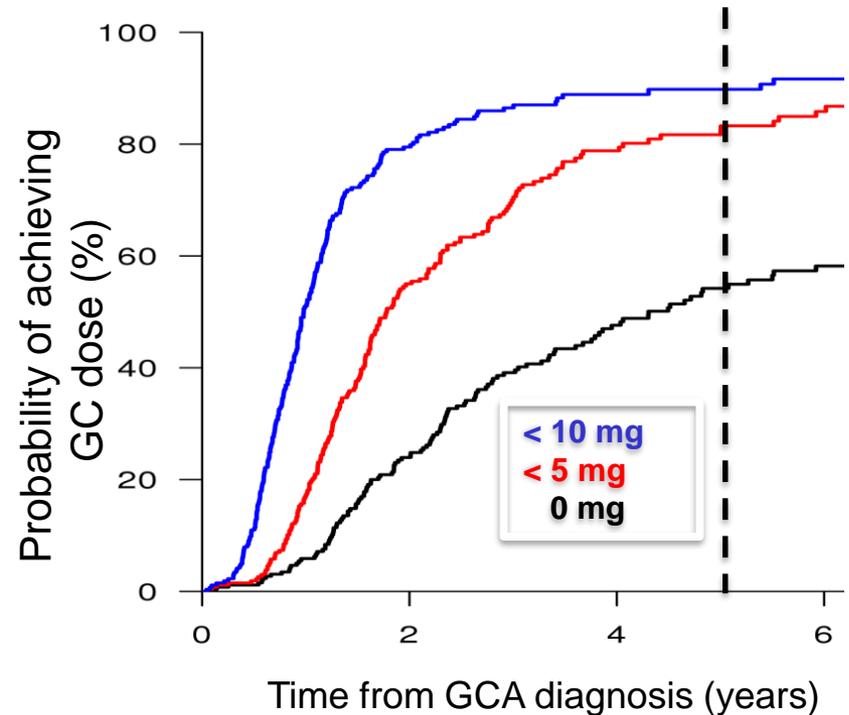
- A. High dose oral prednisone (e.g., 1-2 mg/kg/day)
- B. Pulse steroids (500 mg-1 g/day x 3 days) followed by oral prednisone 1-2 mg/kg/day
- C. Glucocorticoids + methotrexate
- D. Glucocorticoids + tocilizumab
- E. Glucocorticoids + TNF α inhibitor

GCA: Treatment Options

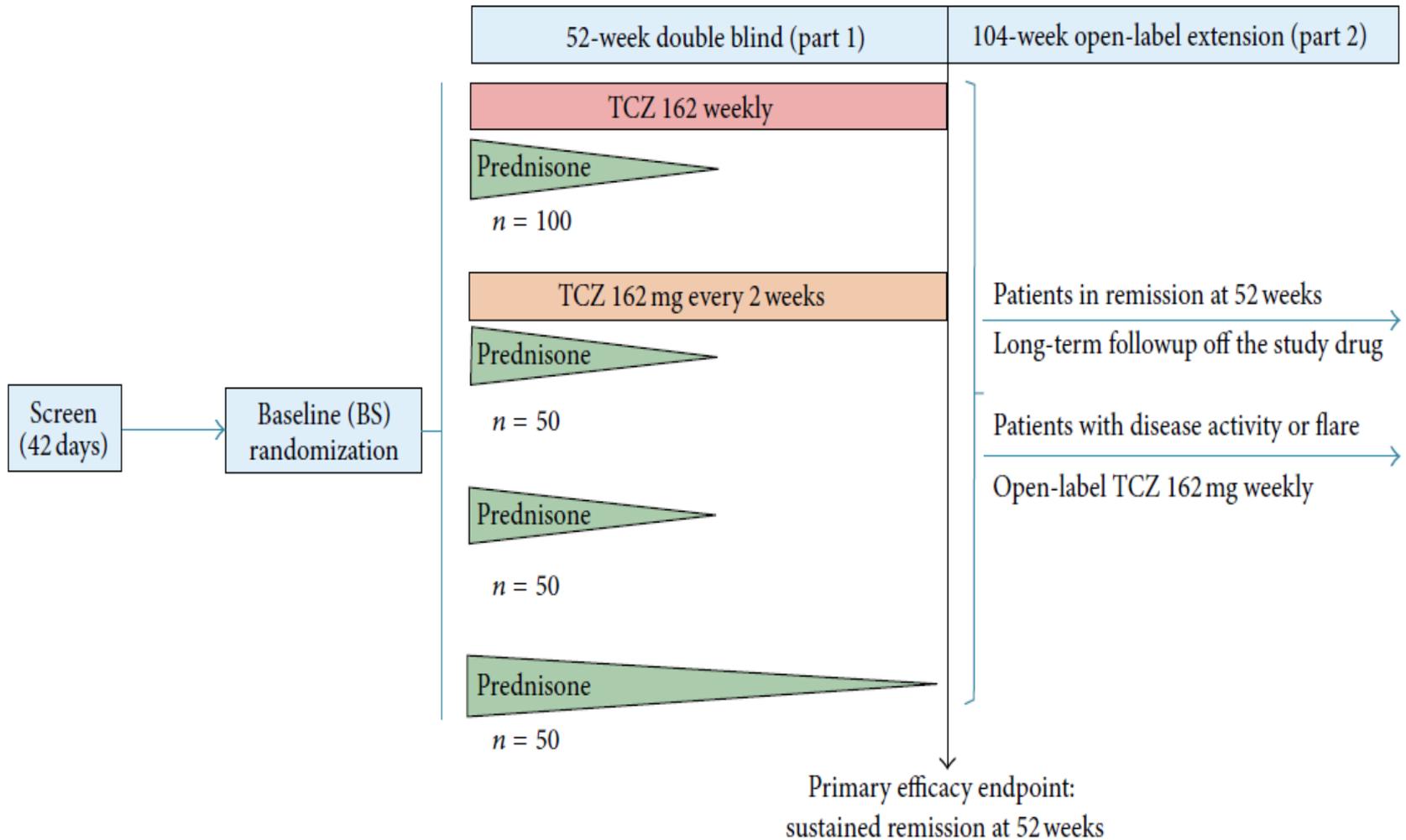
- **Glucocorticoids (GC)**: mainstay of therapy; started early to prevent ischemic complications (start 40-60mg daily)
 - Reconsider diagnosis if no response after 1 week or biopsy negative
 - Conflicting limited data regarding use of pulse GC
 - Taper over months (not years) to minimize complications osteoporosis, infection, DM, cataracts, etc.
- **Tocilizumab**: FDA approved for GCA, steroid sparing
- **Methotrexate**: Modest benefit in meta-analysis, steroid sparing
- **Aspirin**: prevent ischemic complications (with previous cardiac history?)
- Not efficacious in clinical trials: anti-TNF therapy (adalimumab, infliximab, etanercept)

GCA: Treatment course

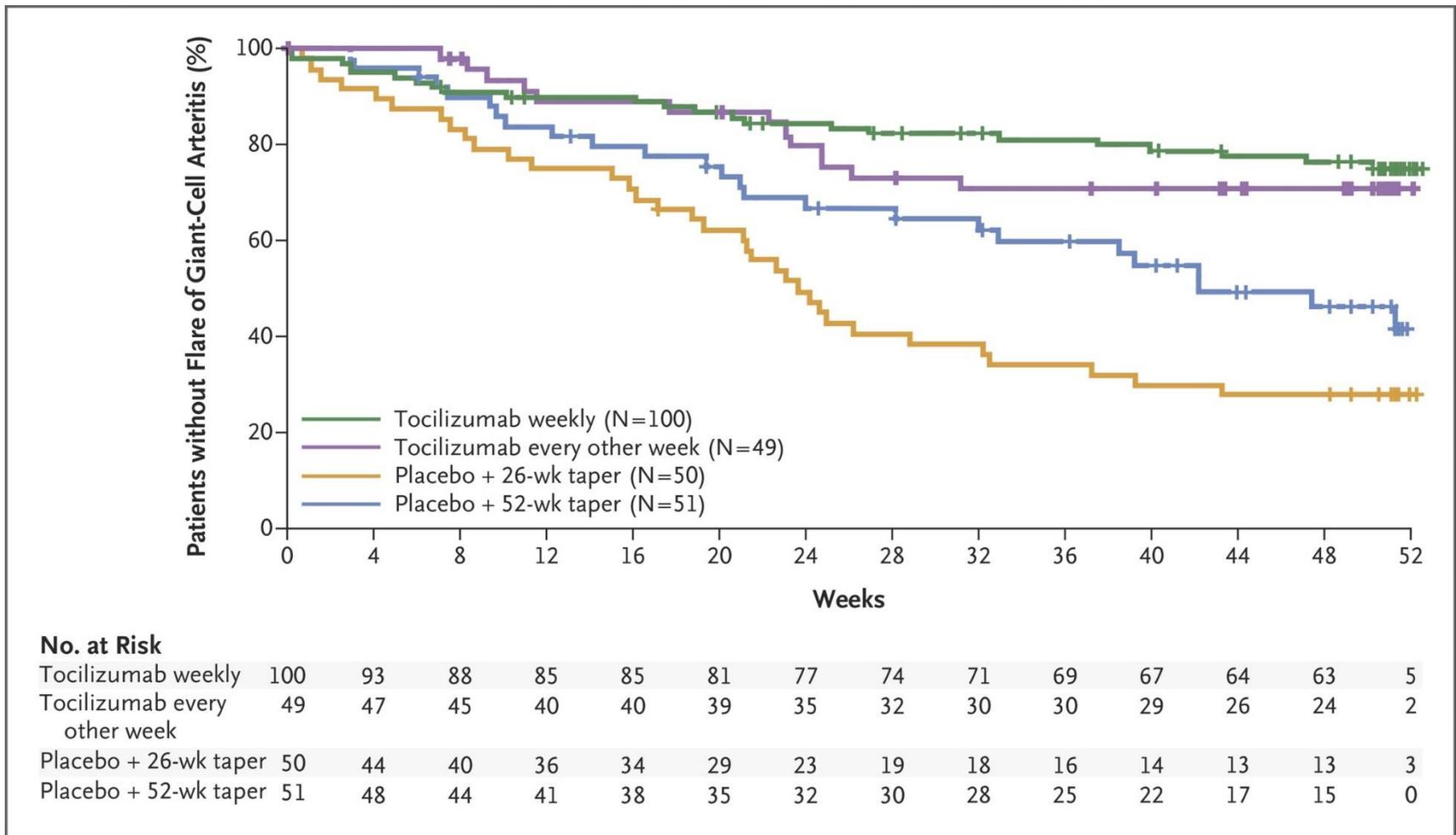
- **Population-based Cohort:**
 - Median duration: 2.1 years
 - 75% off CS after 5 years
- **Referral Cohort:**
 - Discontinuation of GC
 - 24% by 2 years
 - 54% by 5 years



GiACTA: Tocilizumab (TCZ; anti-IL-6)



Time to First Flare after Clinical Remission of Giant-Cell Arteritis in All Patients.



Stone JH et al. N Engl J Med 2017;377:317-328

GiACTA: Results

| Outcome | TCZ weekly + prednisone (6 months) (n=100) | TCZ qo wk + prednisone (6 months) (n=49) | Placebo + prednisone (6 months) (n=50) | p |
|--|--|--|--|--------|
| Sustained remission at 52 weeks, n (%) | 56 (56) | 26 (53) | 7 (14) | <0.001 |
| Cumulative prednisone dose, median (range) | 1862 (630-6602) | 1862 (295-9912) | 3296 (932-9778) | <0.001 |

Safety:

- Similar incidence of infection, injection site reactions
- TCZ: 6 pts developed neutropenia; 1 with anterior ischemic optic neuropathy
- No GI perforations

GiACTA: long-term followup

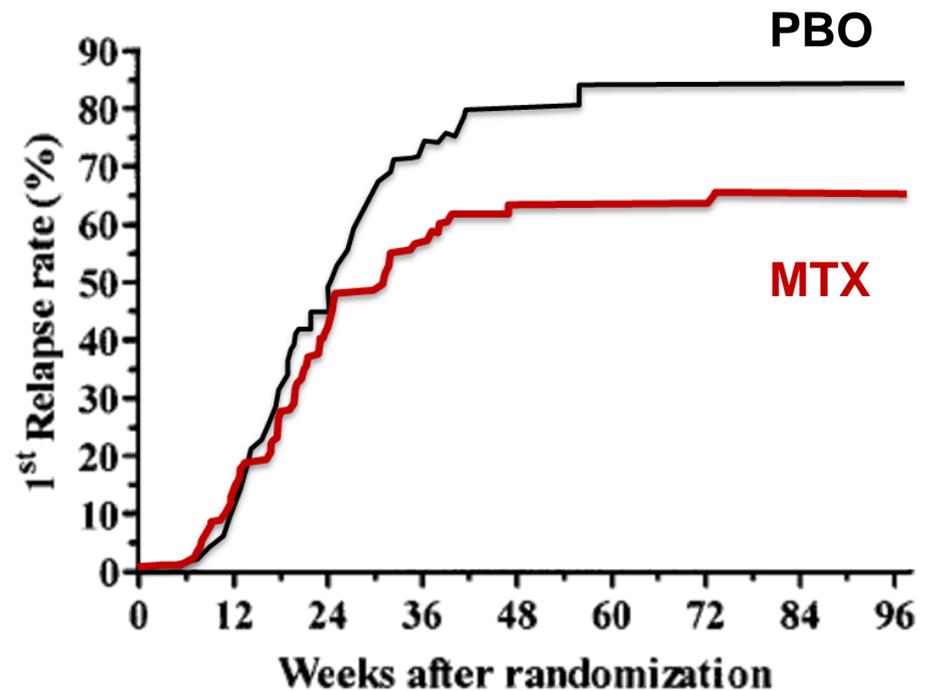
| | TCZ Qweek | TCZ Q2 week | Placebo/ 26 week | Placebo/ 52 week |
|---|--------------|----------------|---------------------|---------------------|
| Maintained CR | 38/81 (47%) | 13/36 (36%) | | |
| Treatment free | 33/51 (65%) | | 17/38 (45%) | |
| Median time to 1 st flare while not on TCZ (days) | 575 | 428 | 162 | 295 |
| Cumulative GC dose over 3 years (median) | 2373 | 2863 | 5006 | 5322 |

- Retreatment with TCZ restore CR in pts who flared
- No additional safety signals observed

Tocilizumab, weekly or every other week, combined with a 26-week prednisone taper was **superior** to either 26-week or 52-week prednisone tapering plus placebo in achieving and maintaining GC-free remission

GCA - Methotrexate

- Meta-analysis (3 randomized trials)
 - 84 on MTX
 - 77 on placebo
- MTX reduced:
 - Risk of 1st relapse by **35%**
 - Risk of 2nd relapse by **51%**
 - Exposure to steroids



Conclusions

- Tocilizumab, weekly or every other week, combined with a 26-week prednisone taper was superior to either 26-week or 52-week prednisone tapering plus placebo
- Longer follow-up is necessary to determine the durability of remission and safety of tocilizumab.

Summary

- GCA is an inflammatory vascular syndrome with feature of cranial and/or large vessel vasculitis, systemic inflammation, and PMR
- GCA and PMR are among the most common rheumatic inflammatory diseases in the elderly; prevalence will increase with our aging population
- Multiple imaging modalities can assist in the diagnosis
- Chronic vessel wall injury and repair can lead to late aneurysm and dissection
- Tocilizimab is now FDA approved as first line therapy for GCA