SUPPLEMENTARY APPENDIX 2: Evidence Report

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

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 1:** In patients with suspected GCA, what is the impact of unilateral versus bilateral temporal artery biopsy on diagnostic accuracy, disease-related outcomes, and tissue biopsy-related adverse events?

- **Critical Outcomes:** Diagnostic accuracy, disease activity, clinical symptoms, damage from disease (e.g., visual loss), pain, scarring, injury to tissue biopsied.

1. In patients with suspected GCA, what is the impact of unilateral versus bilateral temporal artery biopsy on diagnostic accuracy, disease-related outcomes, and tissue biopsy-related adverse events?
   - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Rate of discordant temporal artery biopsy	Durling, 2014	Prospective case-series	Not reported	250 patients	Initial bilateral temporal artery biopsies.	GCA was confirmed in 24.2% (62 of the 250). **Rate of discordant biopsy was 4.4% (11 unilateral positive biopsies)**	-There were 11 unilaterally positive biopsies, representing 17.7% of the total biopsy positive group and 4.4% of the total biopsy population. -Discordance between the localization of symptoms and the side of positive biopsy occurred in 3 patients (i.e., 3 patients had left-sided symptoms, yet a positive right-sided biopsy).
Tissue Biopsy Related Adverse Events	Durling, 2014	Prospective case-series	Not reported	250 patients	Initial bilateral temporal artery biopsies	0.8% (2 patients returned for minor irritation) 0% had no observed cases of infection, unusual bleeding, or seventh nerve injury relating to the biopsy.	- Limited follow-up on patients/ Lack of follow-up time may underestimate rate of TAB related complications. - Patients were all given specific instructions to call and/or return if they had any concerns. Only 2 patients in follow-up returned for temporary minor irritation related to the incision.

*Study includes both arms but not in a comparative manner.							

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies/**Single arm:**

Author	**Year**	**Title**
Durling, B	2014	Incidence of discordant temporal artery biopsy in the diagnosis of giant cell arteritis

- Studies reviewed and excluded:

Author	**Year**	**Title**	**Comments**
K. A. Quinn	2018	Comparison of magnetic resonance angiography and (18)F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis	Mixed patients. No TAB used. Exclude
P. C. Grayson	2018	(18) F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis	Biopsy performed in one patient only. Exclude
A. T. Cristaudo	2016	The impact of temporal artery biopsy on surgical practice	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
K. Le	2015	The effect of temporal artery biopsy on the treatment of temporal arteritis	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
A. Cetinkaya	2008	Intraoperative predictability of temporal artery biopsy results	No outcomes of interest. Exclude
E. W. Chong	2005	Is temporal artery biopsy a worthwhile procedure?	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude

C. P. Au	2016	Increase in the length of superficial temporal artery biopsy over 14 years	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
G. S. Breuer	2009	Rate of discordant findings in bilateral temporal artery biopsy to diagnose giant cell arteritis	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
J. K. Hall	2003	The role of unilateral temporal artery biopsy	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
H. V. Danesh-Meyer	2000	Low diagnostic yield with second biopsies in suspected giant cell arteritis	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
O. Baldursson	1994	Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis	No patient important outcomes for this PICO. Not enough data for diagnostic accuracy outcome. Exclude
M. A. Gonzalez-Gay	1992	Temporal arteritis in a northwestern area of Spain: study of 57 biopsy proven patients	No patient important outcomes for this PICO. Not enough data for diagnostic accuracy outcome. Exclude
R. B. Kent	1990	Temporal artery biopsy	Study does not specify if biopsies were unilateral or bilateral. Exclude
S. Hall	1983	The therapeutic impact of temporal artery biopsy	Study does not distinguish between unilateral and bilateral biopsies. Exclude
Ma Walter	2005	The value of FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease	Irrelevant intervention – no biopsies. Exclude

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 2:** In patients with suspected GCA, what is the impact of a short segment temporal artery biopsy (less than 1 cm) versus a longer biopsy (greater than 1cm) on diagnostic accuracy, disease-related outcomes, and tissue biopsy-related adverse events?

- **Critical Outcomes:** Disease activity, diagnostic accuracy, clinical symptoms, damage from disease (e.g., visual loss), pain, scarring, injury to tissue biopsied.

2. In patients with suspected GCA, what is the impact of a short segment temporal artery biopsy (less than 1 cm) versus a longer biopsy (greater than 1cm) on diagnostic accuracy, disease-related outcomes, and tissue biopsy-related adverse events?
   - No Comparative Data

3. In patients with suspected GCA, what is the impact of a short segment temporal artery biopsy (less than 1 cm) on diagnostic accuracy, disease-related outcomes, and tissue biopsy-related adverse events?
   - No Data Available

4. In patients with suspected GCA, what is the impact a long biopsy (greater than 1 cm) on diagnostic accuracy, disease-related outcomes, and tissue biopsy-related adverse events?
   - No Direct Evidence Available; Indirect Evidence Below:

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Damage from disease: Ischemic Optic Neuropathy; Clinical Symptoms: Vision Loss, Headache	Roth, A 1984	Retrospective Case-Series	Not Reported	51 patients Divided into 3 specimen groups. Group 1à7 patients (13.7%) with abnormal biopsy specimens and clinically responsive to RX. Group 2à 11 patients (21.6%) normal biopsy and clinically responsive to RX. Group 3- 33 (64.7) normal biopsy and clinically unresponsive to RX.	TAB & Steroids (Clinical responsive defined as responsive to steroids with resolution of symptoms within 48 hours and reduction of ESR within three weeks after treatment)	ION in Group 1, 2, 3à 14% [1/7]; 9% [1/11]; 18%[6/33]. Decreased vision: highest in group 3 24% [8/22] vs. Group 1 and 2 14%[1/7] and 18% [2/11], respectively. Headache: 43% [3/7] Group 1; 18% [2/11] Group 2; 45% [15/33] Group 3.	Indirect evidence. All three groups have a mean biopsy length of greater than 1 cm. Group 3 included the group with the highest rate of ION, headache, and vision loss with normal biopsy and no response to treatment (most likely not GCA patients) Since all three groups included a wide range of lengths; [6-25]; [6-28]; [4-24] biopsy length not related to clinical outcomes.
Abnormal Temporal Biopsy	Roth, A 1984	Retrospective Case-Series	Not Reported	As Above	TAB and Steroids.	-Group with biopsy proven abnormalities had the shortest mean specimen length. (Group 1àThe abnormal biopsy group clinically responsive to treatment included a mean length of specimen of 12mm and a range of 6-25 mm.	Indirect evidence, since all three patient groups were suspected of GCA include a mean of >12mm/ “greater than 1 CM”; specimen length not strongly related to diagnostic accuracy of disease vs. response to treatment.

						Group 2à The normal biopsy group with a mean of 17.2 mm and range of 6-28.) -7/51 patients with suspected GCA had abnormal biopsy results. Mean lengthà 12mm; range (6-25)	

- **References:**

- Randomized Controlled Trials:
  None

- Comparative Observational Studies:
  None

- Included Single Arm studies:

Author	Year	Title
Roth, A	1984	The ultimate diagnoses of patients undergoing temporal artery biopsies

- Studies reviewed and excluded:

Some studies assess short segment biopsy but do not present test accuracy results by comparing a short temporal artery biopsy to a reference test, and do not present patient important outcome (like Papadakis et al suggested by the core team: *Papadakis, Marios et al. Temporal artery biopsy in the diagnosis of giant cell arteritis: Bigger is not always better. The American Journal of Surgery, Volume 215, Issue 4, 647 - 650*, where there is information TAB +/- but not data into the length, it's an average length that is very close to 1, so some patients were >1 And some have <1).

Author	Year	Title	Comments
O. Hussain	2016	Diagnosis of giant cell arteritis: when should we biopsy the temporal artery?	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
K. Le	2015	The effect of temporal artery biopsy on the treatment of temporal arteritis	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
A. Cetinkaya	2008	Intraoperative predictability of temporal artery biopsy results	No outcomes of interest. Exclude

C. P. Au	2016	Increase in the length of superficial temporal artery biopsy over 14 years	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
E. Ypsilantis	2011	Importance of specimen length during temporal artery biopsy	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
R. Taylor-Gjevre	2005	Temporal artery biopsy for giant cell arteritis	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
N. Ray-Chaudhuri	2002	Effect of prior steroid treatment on temporal artery biopsy findings in giant cell arteritis	Outomes were not measured by length of biopsies. Exclude
H. V. Danesh-Meyer	2000	Low diagnostic yield with second biopsies in suspected giant cell arteritis	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
O. Baldursson	1994	Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis	No patient important outcomes for this PICO. Not enough data for diagnostic accuracy outcome. Exclude
R. B. Kent	1990	Temporal artery biopsy	Outomes were not measured by length of biopsies. Exclude
R. W. Ikard	1988	Clinical efficacy of temporal artery biopsy in Nashville, Tennessee	No patient important outcomes. Not enough data for diagnostic accuracy outcome. Exclude
Ma Walter	2005	The value of FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease	Irrelevant intervention – no biopsies. Exclude

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 3:** In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy within two weeks of starting oral glucocorticoids versus after two weeks of initiating glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?

- **Critical Outcomes:** Diagnostic Accuracy, Disease activity, Clinical symptoms, Damage from Disease (e.g., visual loss), Serious Adverse Effects, Toxicity Leading to Drug Discontinuation, Pain, Scarring, Injury to tissue biopsied.

5. In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy within two weeks of starting oral glucocorticoids versus after two weeks of initiating glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?
    - **No Comparative Data Avaliable**

6. In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy **within** two weeks of starting oral glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Diagnostic Accuracy treatment within 2 weeks of treatment	Allison, M 1984	Retrospective observational	1 week	Group 1: 51 documented GCA patients received Rx + TAB in 1 week or less. Group 2: 20 received TX + Rx after 1 week.	TAB + Oral Glucocorticoids	82% of 61 patients [group 1 and 2] biopsied before treatment had active histological inflammation. Percentage falls to 60% in the first week of treatment and 10% thereafter. 26/51 (52%) biopsies positive within the first week of treatment. 21/51 (40%) negative within one week of treatment. 4/51 (8%) positive biopsy for atypical arteritis with absent giant cells.	Of the 20 patients in group 2 who had been on prednisolone for more than a week **7/20 were biopsied in the second week.**
	Burry, D 2012	Retrospective observational	< 2 weeks	Group 1: 57 GCA patients 63% (36/57) on steroids for less than 2 weeks at time of TAB. Refined sample: 27/57 GCA patients aged > 50 years with erythrocyte sedimentation rate (ESR) > 50 mm/h at time of TAB. 70% (19/27) on steroids for < 2 weeks.	TAB+ Oral Glucocorticoids	Group 1: (15/36) positivity of biopsy for those on steroids for < [less than] 2 weeks. Stratified sample: 51.9% (11/27) positivity of biopsy group overall. 57% increase in positivity rate (11/19) among steroid patients for less than two weeks. (Use of the American College of Rheumatology criteria better stratifies the likelihood of a positive diagnosis.) -No FP and FN data available; repeat biopsies not done.	For the refined sample: Of the five criteria ACR criteria, they took the two for which we had data (age >50 years and ESR >50 mm/h) and looked at the rates of positive biopsy in the group on steroids for <2 weeks at the time of the biopsy.
	Achkar, 1994	Case series	<2 weeks	535 patients who had a TAB at Mayo Clinic between 1988 and 1991	TAB for GCA (3-4 cm section), 2nd side biopsied if	+TAB findings in 9/32	

					frozen section negative. Retrospectively evaluated prior CS exposure. Used standardized data collection to record information.		

7. In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy **after** two weeks of initiating glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Number of positive TABs (After 4 weeks of treatment)	Chaudhuri, N. 2002	Prospective Observational; Case Series	1 week; at 2-3 weeks; or after 4 weeks	11 Patients meeting the American College of Rheumatology criteria for diagnosis of GCA	Temporal artery biopsy within 1 week, at 2–3 weeks, or after 4 weeks of corticosteroid treatment.	-9 of 11 (82%) patients had positive temporal artery biopsies. **6 of 7 (86%) biopsies performed after 4 or more weeks of steroid treatment were positive.** -6/9 (67%) patients had a positive biopsy after 25 days or more of corticosteroids. -The longest steroid to biopsy interval was 45.	All patients were subsequently confirmed to have GCA clinically on the basis of their presentation, response to steroid treatment, and clinical course.
	Achkar, 1994	Case series	<2 weeks	535 patients who had a TAB at Mayo clinic between 1988 and 1991	TAB for GCA (3-4 cm section), 2nd side biopsied if frozen section negative. Retrospectively evaluated prior CS exposure. Used standardized data collection to record information	+TAB findings in 47/117	

- **References:**

- Randomized controlled trials:
    - None
- Comparative observational studies:
    - None
- Single Arm studies:

Author	Year	Title
Chaudhuri, N	2002	Effect of prior steroid treatment on temporal artery biopsy findings in giant cell arteritis
Allison, M	1984	Temporal artery biopsy and corticosteroid treatment
Burry, D	2012	Does preoperative steroid treatment affect the histology in giant cell (cranial) arteritis?
Ashkar, A	1994	How Does Previous Corticosteroid Treatment Affect the Biopsy Findings in Giant Cell (Temporal) Arteritis?

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 3:** In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy within two weeks of starting oral glucocorticoids versus after two weeks of initiating glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?

- **Critical Outcomes:** Diagnostic Accuracy, Disease activity, Clinical symptoms, Damage from Disease (e.g., visual loss), Serious Adverse Effects, Toxicity Leading to Drug Discontinuation, Pain, Scarring, Injury to tissue biopsied.

8. In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy within two weeks of starting oral glucocorticoids versus after two weeks of initiating glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?
    - **No Comparative Data Avaliable**

9. In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy **within** two weeks of starting oral glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Diagnostic Accuracy treatment within 2 weeks of treatment	Allison, M 1984	Retrospective observational	1 week	Group 1: 51 documented GCA patients received Rx + TAB in 1 week or less. Group 2: 20 received TX + Rx after 1 week.	TAB + Oral Glucocorticoids	82% of 61 patients [group 1 and 2] biopsied before treatment had active histological inflammation. Percentage falls to 60% in the first week of treatment and 10% thereafter. 26/51 (52%) biopsies positive within the first week of treatment. 21/51 (40%) negative within one week of treatment. 4/51 (8%) positive biopsy for atypical arteritis with absent giant cells.	Of the 20 patients in group 2 who had been on prednisolone for more than a week **7/20 were biopsied in the second week.**
	Burry, D 2012	Retrospective observational	< 2 weeks	Group 1: 57 GCA patients 63% (36/57) on steroids for less than 2 weeks at time of TAB. Refined sample: 27/57 GCA patients aged > 50 years with erythrocyte sedimentation rate (ESR) > 50 mm/h at time of TAB. 70% (19/27) on steroids for < 2 weeks.	TAB+ Oral Glucocorticoids	Group 1: (15/36) positivity of biopsy for those on steroids for < [less than] 2 weeks. Stratified sample: 51.9% (11/27) positivity of biopsy group overall. 57% increase in positivity rate (11/19) among Steroid patients for less than two weeks. (Use of the American College of Rheumatology criteria better stratifies the likelihood of a positive diagnosis.) -No FP and FN data available; repeat biopsies not done.	For the refined sample: Of the five criteria ACR criteria, they took the two for which we had data (age >50 years and ESR >50 mm/h) and looked at the rates of positive biopsy in the group on steroids for <2 weeks at the time of the biopsy.
	Achkar, 1994	Case series	<2 weeks	535 patients who had a TAB at Mayo Clinic between 1988 and 1991	TAB for GCA (3-4 cm section), 2nd side biopsied if frozen section negative. Retrospectively	+TAB findings in 9/32	

					evaluated prior CS exposure. Used standardized data collection to record information.		

10. In patients with suspected GCA, what is the impact of obtaining the temporal artery biopsy **after** two weeks of initiating glucocorticoids on diagnostic accuracy, disease-related outcomes, treatment-related adverse events, and tissue biopsy-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Number of positive TABs (After 4 weeks of treatment)	Chaudhuri, N. 2002	Prospective Observational; Case Series	1 week; at 2-3 weeks; or after 4 weeks	11 Patients meeting the American College of Rheumatology criteria for diagnosis of GCA	Temporal artery biopsy within 1 week, at 2–3 weeks, or after 4 weeks of corticosteroid treatment.	-9 of 11 (82%) patients had positive temporal artery biopsies. **6 of 7 (86%) biopsies performed after 4 or more weeks of steroid treatment were positive.** -6/9 (67%) patients had a positive biopsy after 25 days or more of corticosteroids. -The longest steroid to biopsy interval was 45.	All patients were subsequently confirmed to have GCA clinically on the basis of their presentation, response to steroid treatment, and clinical course.
	Achkar, 1994	Case series	<2 weeks	535 patients who had a TAB at Mayo Clinic between 1988 and 1991	TAB for GCA (3-4 cm section), 2nd side biopsied if frozen section negative. Retrospectively evaluated prior CS exposure. Used standardized data collection to record information.	+TAB findings in 47/117	

- **References:**

- Randomized controlled trials:
  - None
- Comparative observational studies:

- None

- Single Arm studies:

Author	Year	Title
Chaudhuri, N	2002	Effect of prior steroid treatment on temporal artery biopsy findings in giant cell arteritis
Allison, M	1984	Temporal artery biopsy and corticosteroid treatment
Burry, D	2012	Does preoperative steroid treatment affect the histology in giant cell (cranial) arteritis?
Ashkar, A	1994	How Does Previous Corticosteroid Treatment Affect the Biopsy Findings in Giant Cell (Temporal) Arteritis?

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 4:** In patients with suspected GCA, what is the impact of utilizing temporal artery ultrasound versus temporal artery biopsy on diagnostic accuracy, disease-related outcomes, and tissue biopsy related-adverse events?

- **Critical Outcomes:** Diagnostic accuracy, Disease activity, Clinical symptoms, Damage from disease (e.g., visual loss, strokes), Pain, Scarring, Injury to tissue biopsied.

11. In patients with suspected GCA, what is the impact of utilizing temporal artery ultrasound versus temporal artery biopsy on diagnostic accuracy, disease-related outcomes, and tissue biopsy related-adverse events?

Certainty assessment							№ of patients		Effect		Certainty Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Color- Duplex Sonography Guided TAB	Standard TAB	Relative (95% CI)	Absolute (95% CI)	
Positive Biopsy Rate in GCA With Classic Transmural Inflammation											
1	randomised trials	not serious	serious	serious [a]	not serious	none	17/50 (34.0%)	10/55 (18.2%)	**OR 1.06** (0.47 to 2.39)	**9 more per 1,000** (from 87 fewer to 165 more)	⨁⨁◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. **This study utilizes ultrasound-guided TAB vs standard TAB**

12. In patients with suspected GCA, what is the impact of utilizing temporal artery ultrasound on diagnostic accuracy, disease-related outcomes, and tissue biopsy related-adverse events?
    - **Test Accuracy Results:** Ultrasound [Halo Sign Alone] of Temporal Artery in GCA cases [based on TAB]:

Author, year	Patient Selection	Risk of bias	Index Test	Risk of bias	Reference Standard	Risk of bias	Flow and timing Rsk of bias	TP	FN	FP	TN	Sens	Spec	PPV/NPV
Reinhard, 2004	Forty-eight patients underwent biopsy of the temporal artery following ultrasound examination.	Low	Standardized ultrasound of temporal artery was performed by one investigator	Not specified if the sonographer was aware of biopsy result	TAB; Unilateral temporal artery was performed in 48 patients.	Not specified if the sonographer was aware of biopsy result	High. Not all patients underwent biopsy	22	11	1	14	67% (22/33)	93% (14/15)	PPV= 96% (22/23); NPV= 56% (14/25)
Black, 2013	50 GCA patients , retrospective chart review	low	75% of cases, ultrasound was performed by one sonographer	Not specified if the sonographer was aware of biopsy result	Temporal artery biopsy was only performed in 21 patients	Not specified if the sonographer was aware of biopsy result	High. Not all patients underwent biopsy	2	3	3	13	40%	81%	PPV = 40% and NPV= 81%
Luqmani	381 patients with newly suspected GCA	low	Biopsy	Low	2-week and 6-month clinical diagnosis	high	low	101	156	0	124	39%	100%	PPV = 100% and NPV = 44%

13. In patients with suspected GCA, what is the impact of temporal artery biopsy on diagnostic accuracy, disease-related outcomes, diagnostic testing-related adverse events, and tissue biopsy-related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Operative complications (390 patients in	Cetinkaya, 2008	Retrospective Single center, one provider	Nov 2002-June 2007	108 patients undergoing TAB for suspected	Temporal artery biopsy, all unilateral	"There were no surgery-related complications."

4 studies had no complications from the temporal artery biopsy, the results are consistent)				GCA(mean age 72.4y, 78 F)		
	Yuksel, 2017	Retrospective, single center	Jan 2011 – Dec 2016	42 patients with GCA diagnosis (ACR 1990 criteria) who underwent TAB (20F, mean age 66y)	Temporal artery biopsy, unilateral in all but 2 patients	"No complications were observed postoperatively."
	Hedgers, 1983	Retrospective, single center	Jan 1968 - Dec 1978	193 patients who underwent TAB.	Temporal artery biopsy, at least 1cm artery (no specifics on unilaterality)	"No complications occurred from any of the biopsy procedures done on patients in the study group, and we are unaware of any occurring in the 193 patients who underwent a biopsy."
	Goslin, 2011	Retrospective, single center	Jul 1997-Jun 2007	47 patients underwent 53 TAB	Mean length 1.42cm	"There were not complications with short term, in-hospital follow up."

- **Test Accuracy results:**

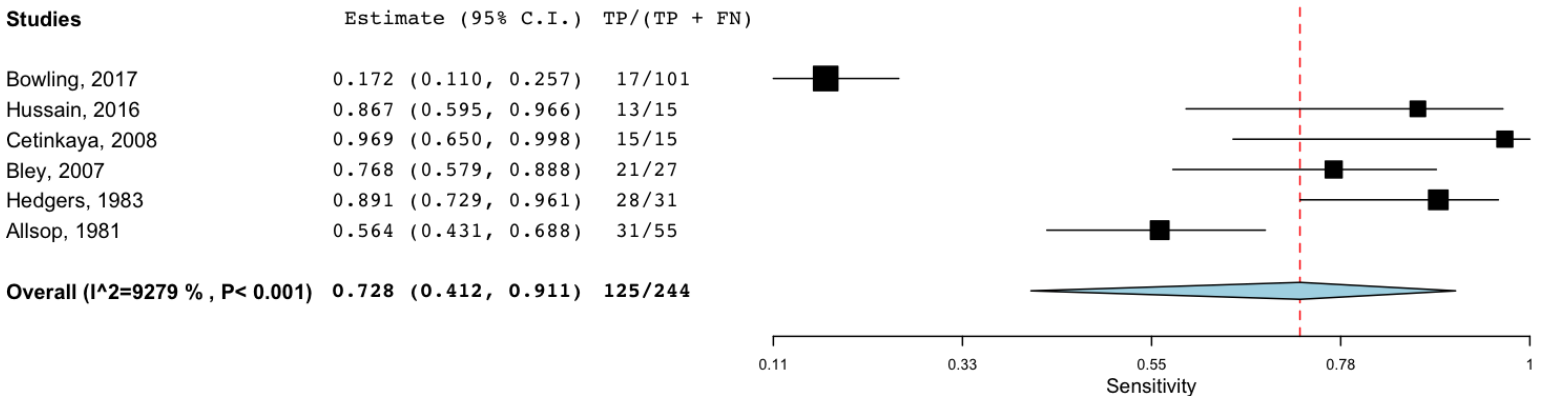
Sensitivity	0.73 (95% CI: 0.41 to 0.91)
Specificity	0.94 (95% CI: 0.68 to 0.99)

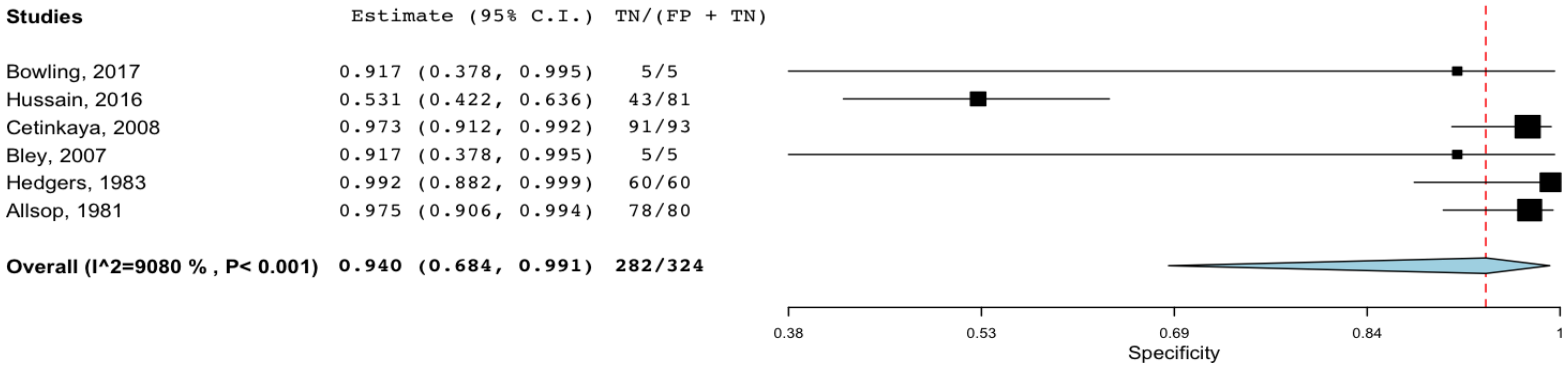
Prevalence	20%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives (patients with Giant cell arteritis)	6 studies 244 patients	cohort & case-control type studies	serious [a]	not serious	very serious [b]	very serious [c]	none	146 (82 to 182)	364 (206 to 456)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having Giant cell arteritis)								54 (18 to 118)	136 (44 to 294)	
True negatives (patients without Giant cell arteritis)	6 studies 324 patients	cohort & case-control type studies	serious [a]	not serious	very serious [d]	serious [e]	none	752 (547 to 793)	470 (342 to 496)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having Giant cell arteritis)								48 (7 to 253)	30 (4 to 158)	

- **Explanations**

- a. the index test results were interpreted with knowledge of the results of the reference standard, the reference standard results were interpreted with knowledge of the results of the index test
- b. The pooled sensitivity does not cross the confidence interval in Bowling, 2017. the measure of heterogeneity I2= 93%.
- c. The pooled sensitivity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.
- d. The pooled specificity does not cross the confidence interval in Hussein, 2016. the measure of heterogeneity I2= 91%.
- e. The pooled specificity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.





- **References:**

- Randomized controlled trials:

Author	Year	Title
Germano, G.	2015	Is colour duplex sonography-guided temporal artery biopsy useful in the diagnosis of giant cell arteritis? A randomized study

- Comparative observational studies:
  None

- Single arm and Test Accuracy studies:

	Author	**Year**	**Title**

Test accuracy results	Bowling	2017	Temporal artery biopsy in the diagnosis of giant cell arteritis: Does the end justify the means?
	Hussain	2016	Diagnosis of giant cell arteritis: when should we biopsy the temporal artery?
	Bley	2007	Diagnostic value of high-resolution MR imaging in giant cell arteritis
	Allsop	1981	Temporal artery biopsy in giant-cell arteritis. A reappraisal
	Black, R.	2013	The use of temporal artery ultrasound in the diagnosis of giant cell arteritis in routine practice
	Reinhard, M	2004	Color-coded sonography in suspected temporal arteritis-experiences after 83 cases
	Luqmani	2016	The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study
Patients important outcomes	Yuksel	2017	Clinical correlation of biopsy results in patients with temporal arteritis
	Goslin	2011	Temporal artery biopsy as a means of diagnosing giant cell arteritis: is there over-utilization?
	Cetinkaya	2008	Intraoperative predictability of temporal artery biopsy results
	Hedges	1983	The clinical value of negative temporal artery biopsy specimens

Studies reviewed and excluded:

Author	**Year**	**Title**	**Comment**
D. M. Nuenninghoff	2003	Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years	Exclude. Incidence study. Does not address any arm of PICO question
A. W. Stanson	2000	Imaging findings in extracranial (giant cell) temporal arteritis	Exclude. Review article
D. Blockmans	2000	Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch	Exclude. Study did not specify GCA and PMR results
A. Brack	1999	Disease pattern in cranial and large-vessel giant cell arteritis	Exclude. Does not address any arm of PICO question

J. R. Sewell	1980	Combined temporal arteriography and selective biopsy in suspected giant cell arteritis	Exclude. Temporal arteriography is not utilized anymore in clinical practice

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 5:** In patients with suspected GCA, what is the impact of temporal artery MRI versus temporal artery biopsy on diagnostic accuracy, disease-related outcomes, diagnostic testing-related adverse events, and tissue biopsy-related adverse events?

- **Critical Outcomes:** Disease activity, clinical symptoms, damage from disease (e.g., visual loss, strokes), pain, scarring, injury to tissue biopsied, adverse reaction to contrast exposure (e.g., Gadolinium).

14. In patients with suspected GCA, what is the impact of temporal artery MRI versus temporal artery biopsy on diagnostic accuracy, disease-related outcomes, diagnostic testing-related adverse events, and tissue biopsy-related adverse events?
    - No comparative data available

15. In patients with suspected GCA, what is the impact of temporal artery MRI on diagnostic accuracy, disease-related outcomes, diagnostic testing-related adverse events, and tissue biopsy-related adverse events?
    - **Test Accuracy results:** Reference test is clinical diagnosis

Sensitivity	0.73 (95% CI: 0.60 to 0.83)
Specificity	0.88 (95% CI: 0.82 to 0.92)

Prevalence	55%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 55%	
True positives (patients with Giant Cell arteritis)	7 studies 216 patients	cohort & case-control type studies	not serious	not serious	serious [a]	serious [b]	none	403 (329 to 459)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having Giant Cell arteritis)								147 (91 to 221)	
True negatives (patients without Giant Cell arteritis)	7 studies 179 patients	cohort & case-control type studies	not serious	not serious	not serious	very serious [c]	none	395 (367 to 414)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having Giant Cell arteritis)								55 (36 to 83)	

- **Explanations**
- a. The pooled sensitivity does not cross the confidence interval in Guinoi, 2008. the measure of heterogeneity I2= 63%.
- b. The pooled sensitivity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.
- c. The pooled specificity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.

- **Test Accuracy results:** Reference test is temporal artery biopsy

Sensitivity	0.82 (95% CI: 0.64 to 0.93)
Specificity	0.74 (95% CI: 0.63 to 0.82)

Prevalence	55%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 55%	
True positives (patients with Giant Cell arteritis)	6 studies 135 patients	cohort & case-control type studies	not serious	not serious	serious [a]	serious [b]	none	454 (349 to 510)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having Giant Cell arteritis)								96 (40 to 201)	
True negatives (patients without Giant Cell arteritis)	6 studies 85 patients	cohort & case-control type studies	not serious	not serious	not serious	very serious [c]	none	332 (284 to 369)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having Giant Cell arteritis)								118 (81 to 166)	

- **Explanations**
- a. The pooled sensitivity does not cross the confidence interval in Guinoi, 2008. the measure of heterogeneity I2= 69%.
- b. The pooled sensitivity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.
- c. The pooled specificity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.

16. In patients with suspected GCA, what is the impact of temporal artery biopsy on diagnostic accuracy, disease-related outcomes, diagnostic testing-related adverse events, and tissue biopsy-related adverse events?

- **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Operative complications (390 patients in 4 studies had no	Cetinkaya, 2008	Retrospective Single center, one provider	Nov 2002-June 2007	108 patients undergoing TAB for suspected GCA(mean age 72.4y, 78 F)	Temporal artery biopsy, all unilateral	"There were no surgery-related complications."

complications from the temporal artery biopsy, the results are consistent)	Yuksel, 2017	Retrospective, single center	Jan 2011 – Dec 2016	42 patients with GCA diagnosis (ACR 1990 criteria) who underwent TAB (20F, mean age 66y)	Temporal artery biopsy, unilateral in all but 2 patients	"No complications were observed postoperatively."
	Hedgers, 1983	Retrospective, single center	Jan 1968 - Dec 1978	193 patients who underwent TAB.	Temporal artery biopsy, at least 1cm artery (no specifics on unilaterality)	"No complications occurred from any of the biopsy procedures done on patients in the study group, and we are unaware of any occurring in the 193 patients who underwent a biopsy."
	Goslin, 2011	Retrospective, single center	Jul 1997-Jun 2007	47 patients underwent 53 TAB	Mean length 1.42cm	"There were not complications with short term, in-hospital follow up."

- **Test Accuracy results:**

Sensitivity	0.73 (95% CI: 0.41 to 0.91)
Specificity	0.94 (95% CI: 0.68 to 0.99)

Prevalence	20%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives (patients with Giant cell arteritis)	0 studies patients	cohort & case-control type studies	serious [a]	not serious	very serious [b]	very serious [c]	none	146 (82 to 182)	364 (206 to 456)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having Giant cell arteritis)								54 (18 to 118)	136 (44 to 294)	
True negatives (patients without Giant cell arteritis)	0 studies patients	cohort & case-control type studies	serious [a]	not serious	very serious [d]	serious [e]	none	752 (547 to 793)	470 (342 to 496)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having Giant cell arteritis)								48 (7 to 253)	30 (4 to 158)	

- **Explanations**
- a. The index test results were interpreted with knowledge of the results of the reference standard, the reference standard results were interpreted with knowledge of the results of the index test
- b. The pooled sensitivity does not cross the confidence interval in Bowling, 2017. the measure of heterogeneity I2= 93%.
- c. The pooled sensitivity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.
- d. The pooled specificity does not cross the confidence interval in Hussein, 2016. the measure of heterogeneity I2= 91%.
- e. The pooled specificity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

	Author	**Year**	**Title**
Test accuracy results	Bowling	2017	Temporal artery biopsy in the diagnosis of giant cell arteritis: Does the end justify the means?
	Hussain	2016	Diagnosis of giant cell arteritis: when should we biopsy the temporal artery?
	Klink	2014	Giant cell arteritis: diagnostic accuracy of MR imaging of superficial cranial arteries in initial diagnosis-results from a multicenter trial
	Hauenstein	2012	Effects of early corticosteroid treatment on magnetic resonance imaging and ultrasonography findings in giant cell arteritis
	Ghinoi	2008	1T magnetic resonance imaging in the diagnosis of giant cell arteritis: comparison with ultrasonography and physical examination of temporal arteries
	Bley	2007	Diagnostic value of high-resolution MR imaging in giant cell arteritis
	Bley	2005	Assessment of the cranial involvement pattern of giant cell arteritis with 3T magnetic resonance imaging
	Allsop	1981	Temporal artery biopsy in giant-cell arteritis. A reappraisal
	Bley	2008	Comparison of duplex sonography and high-resolution magnetic resonance imaging in the diagnosis of giant cell (temporal) arteritis
Patients important outcomes	Yuksel	2017	Clinical correlation of biopsy results in patients with temporal arteritis
	Goslin	2011	Temporal artery biopsy as a means of diagnosing giant cell arteritis: is there over-utilization?

	Cetinkaya	2008	Intraoperative predictability of temporal artery biopsy results
	Hedges	1983	The clinical value of negative temporal artery biopsy specimens

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 6:** In patients with suspected GCA, what is the impact of imaging the large vessels versus clinical assessment alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related complications?

- **Critical Outcomes:** Disease activity, clinical symptoms, damage from disease (e.g., Ischemic limbs), adverse reaction to contrast exposure including nephrotoxicity, death

17. In patients with suspected GCA, what is the impact of imaging the large vessels versus clinical assessment alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related complications?
    - No Comparative Data Available

18. In patients with suspected GCA, what is the impact of imaging the large vessels on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related complications?
    - **Patient Important Outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity; Ultrasound	Schmidt, 2008	Case-control	9 years	176 GCA patients	Ultrasound of temporal artery, axillary artery, subclavian artery, proximal brachial artery	30% of patients showed ultrasound changes. Temporal artery (62%), Axillary artery (98%), subclavian artery (61%), proximal brachial artery (21%). Findings were bilateral in 79%.	
Diagnostic accuracy; FDG-PET vs US	Pfadenhauer, 2011	Observational cohort	Not reported	46 GCA patients	FDG-PET imaging of vertebral arteries as	**33%** (15/46) of GCA patients with abnormal PET findings	Extracranial vertebral arteries are a

					compared to ultrasound and biopsy	had high FDG uptake within the vertebral artery. Ultrasonography found **22%** (10/46) PET is superior to ultrasound in detecting vertebral artery abnormalities in active GCA	good target for PET imaging.
Disease Activity; FDG-PET/CT; MRI MRA 2 studies used FDG-PET at baseline/before treatment. FDG-PET included a higher sensitivity in patients with high CRP vs ESR. MRA and FDG-PET overall agreement is 72%. Steroids significantly reduces the diagnostic accuracy of FDG-PET after 10 days of treatment with	Blockmans, 2006	Retrospective	3 years	35 GCA patients	FDG-PET before treatment, 3 mos after treatment, 6 mos after treatment	FDG uptake noted in 83% of patients. Subclavian (74%), thoracic aorta (51%), abdominal aorta (54%), Femoral artery (37%)	Total vascular score (TVC) decreased significantly after 3 months of steroid treatment ($p<0.0005$). but did not further decrease at 6 months
	Aide, 2017	Retrospective, chart review	62 months	25 GCA patients with positive FDG PET/CT at baseline	FDG PET/CT were done at baseline, then **after 3 months of clinically controlled disease**	On follow up second scan showed: 16% (4/25) had negative scan, 32% (8/25) had decreased uptake, 40% (10/25) had unchanged uptake, 12% (3/25) had worsening uptake. **In total, 21/25 (84%) of patients FDG PET/CT remained positive on repeat scan despite clinically controlled disease with glucocorticoids**	
	Walter, 2005	Prospective observational	24 months	20 consecutive GCA patients, classified using ACR criteria	FDG PET, visually graded using four-point scale	Analysis in those with a **high ESR** revealed a sensitivity of 78.6% for patients suffering from GCA.	Study mostly combined the data on GCA and TAK.

a diagnostic window of 3 days.						Analysis in those with a **high CRP** revealed a sensitivity of 93.7%f or patients suffering from GCA.	Only presented **sensitivity** data separately on GCA and TAK
	Both, 2008	Observational, cross sectional	Cross sectional	25 GCA patients with complicated course of disease despite immunosuppressive therapy	MRI, thoracic FDG-PET and whole body FDG-PET	**Active disease as detected by MRI in 88% (22/25)** , thoracic FDG-PET 56% (14/25), and whole body FDG-PET 80% (20/25) patients. There was no concordance with MRI and BVAS.2 (R_2 = -0.064, p= 0.76), **weak correlation of whole body PET with BVAS.2 (R_2=0.258, p=0.21)**	Enrolled GCA patients had persistent disease despite treatment
	Quinn, 2018	Prospective, observational cohort	Not indicated	84 patients w LVV, but only 35 patients with GCA	MRA, FDG-PET	GCA patients: **Overall agreement between MRA and FDG-PET is 72%,** Cohen's kappa=0.27	
	Nielsen, 2017	Prospective	2 years	24 newly diagnosed GCA patients. Patient were treated with prednisone 60 mg	FDG-PET	Large vessel GCA was accurately diagnosed in 10/10 patients after 3 days of treatment, but **only in 5/14 patients after 10 days of treatment** (p< 0.001)	Diagnostic window of 3 days vs. a dramatic decline in 10 days.

Disease Activity; New arterial lesions.	Kermani, 2018	Prospective, multicenter, longitudinal study	8 years	187 GCA pts	Type of imaging study was MRA (72%), CTA (27%) and conventional angiography (1%) 50 patients (27%) were enrolled in the AGATA clinical trial with regular imaging per protocol.	66% of patients with GCA had at least one arterial lesion on first imaging study. By 2 years, 33% of patients had developed a new arterial lesion. -Use of immunosuppressive therapy at entry into the cohort was associated with lower risk of new arterial lesions (p=0.038). -All of the new lesions in this study occurred among patients who had abnormalities on first imaging. Only 40–50% of visits with a new lesion had any symptoms of active disease in the preceding months	For the longitudinal study, the decision regarding timing and type of imaging study was left to the discretion of the treating physician.

- **Test Accuracy Results:** Ultrasound [Halo Sign Alone] of Temporal Artery in GCA cases [based on TAB]:

Author, year	Patient Selection	Risk of bias	Index Test	Risk of bias	Reference Standard	Risk of bias	Flow and timing Rsk of bias	TP	FN	FP	TN	Sens	Spec	PPV/NPV
Reinhard, 2004	Forty-eight patients underwent biopsy of the temporal artery following	Low	Standardized ultrasound of temporal artery was performed	Not specified if the sonographer was aware of biopsy result	TAB; Unilateral temporal artery was performed in 48 patients.	Not specified if the sonographer was aware	High. Not all patients underwent biopsy	22	11	1	14	67% (22/33)	93% (14/15)	PPV= 96% (22/23); NPV=

	ultrasound examination.		by one investigator			of biopsy result								56% (14/25)
Black, 2013	50 GCA patients, retrospective chart review	low	75% of cases, ultrasound was performed by one sonographer	Not specified if the sonographer was aware of biopsy result	Temporal artery biopsy was only performed in 21 patients	Not specified if the sonographer was aware of biopsy result	High. Not all patients underwent biopsy	2	3	3	13	40%	81%	PPV = 40% and NPV= 81%

- **Test Accuracy Results:** CT/PET of Temporal Artery in GCA cases [based on TAB]:

Sammel, 2019	This is a study of 64 patients who underwent TAB, 12 were positive on pathology. 21 had clinical dx of GCA.	Low	Patients underwent CT/PET	Low, double blinded	Temporal artery biopsy was performed in 58 patients	Low, double blinded	High. Not all patients underwent biopsy	11	1	7	39	92%	85%	PPV = 61% And NPV = 98%
Fuchs, 2012	30 patients with suspected large vessel Vasculitis (24 GCA, 6 TAK)	Low	18F-FDG PET	Low	Expert panel assessment based on ACR criteria from 1990	High	Low	22	8	5	26	73.3%	83.3%	PPV = 88% And NPV = 77%

19. In patients with suspected GCA, what is the impact of clinical assessment alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related complications?
    - No single arm or test accuracy data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

Patient Important Outcomes	Author	Year	Title
	Quinn, K.	2018	Comparison of magnetic resonance angiography and (18)F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis

	Kermani, T.	2018	Arterial lesions in giant cell arteritis: A longitudinal study
	Nielsen, B.	2017	Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy
	Pfadenhauer, K.	2011	Vertebral arteries: a target for FDG-PET imaging in giant cell arteritis? Clinical, ultrasonographic and PET study in 46 patients
	Schmidt, W.	2008	Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis
	Blockmans, D.	2006	Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients
	Aide, H.	2017	Repetitive (18)F-FDG-PET/CT in patients with large-vessel giant-cell arteritis and controlled disease
	Walter, M.	2005	The value of FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease
	Both, M	2008	MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis
Test Accuracy	Black, R.	2013	The use of temporal artery ultrasound in the diagnosis of giant cell arteritis in routine practice
	Reinhard, M	2004	Color-coded sonography in suspected temporal arteritis-experiences after 83 cases
	Sammel, A	2019	Diagnostic Accuracy of Positron Emission Tomography/Computed Tomography of the Head, Neck, and Chest for Giant Cell Arteritis: A Prospective, Double-Blind, Cross-Sectional Study.
	Fuchs	2012	The impact of 18F-FDG PET on the management of patients with suspected large vessel vasculitis

- Studies reviewed and excluded:

Author	**Year**	**Title**	**Comments**
P. C. Grayson	2018	(18) F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis	Exclude. Test accuracy study were done collectively for “Large Vessel Vasculitis (GCA+TAK).” Not able to determine the outcome for GCA specifically.
K. M. Treitl	2017	3D-black-blood 3T-MRI for the diagnosis of thoracic large vessel vasculitis: A feasibility study	Exclude. Study was done collectively for “Large Vessel Vasculitis (GCA+TAK).” Not able to determine the outcome for GCA specifically.

P. C. Grayson	2012	Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis	Exclude. Test accuracy study were done collectively for "Large Vessel Vasculitis (GCA+TAK)." Not able to determine the outcome for GCA specifically.
J. C. Henes	2007	[18F] FDG-PET/CT as a new and sensitive imaging method for the diagnosis of large vessel vasculitis	Exclude. Mostly descriptive data only. No outcome analysis done.
C. Lavado-Perez	2015	(18)F-FDG PET/CT for the detection of large vessel vasculitis in patients with polymyalgia rheumatica	Exclude. Wrong population. Study on PMR patients
D. M. Nuenninghoff	2003	Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years	Exclude. Incidence study. Does not address any arm of PICO question
A. W. Stanson	2000	Imaging findings in extracranial (giant cell) temporal arteritis	Exclude. Review article
D. Blockmans	2000	Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch	Exclude. Study did not specify GCA and PMR results
A. Brack	1999	Disease pattern in cranial and large-vessel giant cell arteritis	Exclude. Does not address any arm of PICO question
J. R. Sewell	1980	Combined temporal arteriography and selective biopsy in suspected giant cell arteritis	Exclude. Temporal arteriography is not utilized anymore in clinical practice
L. F. Layfer	1978	Temporal arteriography. Analysis of 21 cases and a review of the literature	Exclude. Temporal arteriography is not utilized anymore in clinical practice
H. M. Horwitz	1977	Temporal arteriography and immunofluorescence as diagnostic tools in temporal arteritis	Exclude. Temporal arteriography is not utilized anymore in clinical practice
R. G. Klein	1975	Large artery involvement in giant cell (temporal) arteritis	Exclude. Does not address any arm of PICO question
J. C. Henes	2008	[18F] FDG-PET/CT as a new and sensitive imaging method for the diagnosis of large vessel vasculitis	Exclude. Mostly descriptive data only. No outcome analysis done.
T. Ponge	1988	The efficacy of selective unilateral temporal artery biopsy versus bilateral biopsies for diagnosis of giant cell arteritis	Exclude. Does not address any arm of PICO 6. More appropriate for PICO on Temporal artery biopsy

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 7:** In patients with suspected GCA and a negative temporal artery biopsy, what is the impact of large vessel imaging versus clinical assessment alone on diagnostic accuracy, disease-related outcomes, and diagnostic-tested related adverse events?

- **Critical Outcomes**: Disease activity, clinical symptoms, damage from disease (e.g., visual loss, strokes), serious adverse effects, adverse reaction to contrast exposure including nephrotoxicity

20. In patients with suspected GCA and a negative temporal artery biopsy, what is the impact of large vessel imaging versus clinical assessment alone on diagnostic accuracy, disease-related outcomes, and diagnostic-tested related adverse events?
    - No Comparative Data Available.

21. In patients with suspected GCA and a negative temporal artery biopsy, what is the impact of large vessel imaging on diagnostic accuracy, disease-related outcomes, and diagnostic-tested related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Ability of PET to diagnosis GCA in pts with neg TA bx	Ray B, 2019	Retrospective study in a cohort of patients with suspected GCA and negative TAB who underwent an ^{18}F-FDG PET-CT.	f/u of at least 18 months 2007 - 2017		Ten vascular segments were studied using a visual score and a semi-quantitative method based on SUVmax ratio with respect to liver uptake. The diagnosis of GCA was established during a mean follow-up of 42 months, based on the presence of clinical symptoms, laboratory results, and imaging	63 patients (30 men and 33 women, aged 67 ± 12 years) included. F-FDG PET-CT showed large vessel involvement in 22 pts, 14 of whom were diagnosed with GCA. Forty-one pts were ^{18}F-FDG PET-CT negative, 9 of whom were diagnosed with GCA	A significant number of patients were treated by corticosteroids before ^{18}F-FDG PET-CT. However, corticosteroid therapy did not impact significantly the diagnostic performance, although there was a trend to a lower sensitivity in patients receiving

					data compatible with GCA, good response to corticosteroid therapy, and no differential diagnosis after a follow-up of at least 18 months.	Sixteen patients (25%) received corticosteroid therapy before TAB (median time 10 days, and more than 2 weeks before TAB in 7 cases). Twenty-six patients (41%) received corticosteroid therapy before F-FDG PET-CT (median time 92 days, and more than 3 days before F-FDG PET- CT in 24 cases).	corticosteroid therapy for more than 3 days. Importantly, corticosteroid therapy can negatively affect the sensitivity of -FDG PET-CT in large vessel vasculitis. If treatment has to be started -FDG PET-CT should be performed as soon as possible (ideally within 3 days of treatment) to lessen the risk of false-negative results.

22. In patients with suspected GCA and a negative temporal artery biopsy, what is the impact of clinical assessment alone on diagnostic accuracy, disease-related outcomes, and diagnostic-tested related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population)	Intervention used in relevant population	Results
Disease Activity	Le K, 2015	Retrospective analysis, single center 2003-2010	Not specified	237 patients with suspected GCA who underwent TAB. Sx's included new onset HA (75%), auricular tenderness/jaw claud (32%), ESR>50 (60%), 3 or more ACR criteria (56%)	Evaluation of positive or negative biopsies in suspected GCA. Looked at association with length of biopsy, pre-op steroids, and decision to treat	**Biopsy results had no significant impact on subsequent treatment in 69% of patients who met clinical criteria.** Among 56% of patients who met criteria for clinical diagnosis of TA, only 22% demonstrated a positive biopsy. 93% sensitivity of diagnosis of GCA using ACR criteria not including results of TAB.

	Hall S, 1983	Retrospective study of 134 patients in olmstead county who underwent TAB between 1965-1980	Medial follow up of 70 months (1-192)	134 patients underwent TAB, 46 were positive, 88 were negative, 8 of the 88 neg TAB diagnosed with GCA and tx's with long term steroids	Neg TAB patients were comparable with + group in clinical features (PMR, malaise, fevers, weight loss, HA, visual disturbance.	Hx of jaw pain or claudication or clinically abnormal TA, more common in positive biopsy group. In 8 patients with neg TAB, dx of GCA made based on pathologic/radiologic or convincing clinical evidence. Other dx included infection, CTD, malignancy. Of 8 negative TAB pts diagnosed with GCA, 62% (5/8) satisfied at least 4 other ACR criteria and treated with regular steroid course. 1 had repeat biopsy 8 months later positive; 1 patients treated with NSAIDS for 15 months, then found to have LV involvement; 1 patient developed TAA treated with high dose CS and then died of aortic rupture.
Clinical Symptoms	Breuer G, 2008	Retrospective review of 58 biopsy negative suspected GCA patients	6 months after biopsy	58 patients with negative TAB included.	Biopsy negative GCA diagnosed when classification criteria was met: symptoms improved within 3 days of steroid therapy, and no other condition relevant to the patients sx's diagnosed during a 6 month follow up.	**Headaches were more common in biopsy negative GCA patients (91% compared to only 40% of non GCA patients).** Biopsy negative GCA diagnosed in 19% (11/58), 7 had other rheumatologic diseases, 60% had non-rheumatologic disease.
	Sorenson S, 1977	Retrospective Study	1-24 months	63 patients with GCA or PMR. Collected over 10 year period (1964-73)	Histologic examination of 58 patients with symptoms.	Histologic examination of 58 patients revealed arteritis in 46. Biopsy negative findings found in 19% (12/63) of which 91.6% (11/12) had Myalgia without local symptoms of temporal arteritis and 1 patient with local symptoms of TA without myalgia.
Complications of RX in Negative TAB GCA Examples include fractures, DM, pulmonary infections as well as peptic ulcer disease.	Gonzalez-Gay M, 2001	Retrospective study of an unselected population of patients with GCA diagnosed at the reference hospital between 1981-1998.	From time of diagnosis until death or October 1999. All patients observed for at least 1 year *median duration 3.5 years	190 patients with GCA, 29 (15.3%) had negative TAB. No change in diagnosis.	Neg TAB GCA patients evaluated for therapeutics, side effects and duration of treatment	No case of blindness after treatment started Severe side effects (fracture 2/2 osteoporosis, DM or pulmonary infections occurred in 6/29

			(range 1-14)			
Disease-Related Complications in TAB negative GCA	Hedgers T, 1983	Retrospective study of 193 patients who had TAB at one center between 1968-1978 with available clinical data in 91 cases.	At least 2 years	70% (63/91) patients had negative TAB	All TAB specimens reviewed for e/o granulomatous inflammation, re-reviewed and scored for atherosclerotic changes and various clinical and lab findings compared between groups	Diabetes occurred in 20% of patients without arteritis and 10% of those with arteritis. Of 42 patients with both negative and positive biopsy specimens treated for 1 or more months with steroids, 12% (5/42) developed peptic ulcer disease and 1 had a compression fracture.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

	Author	Year	Title
Patient important Outcomes	Le, K	2015	The effect of temporal artery biopsy on the treatment of temporal arteritis
	Breuer, G	2008	Negative temporal artery biopsies: eventual diagnoses and features of patients with biopsy-negative giant cell arteritis compared to patients without arteritis
	Gonzalez-Gay, M	2001	Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy
	Hall, S	1983	The therapeutic impact of temporal artery biopsy
	Hedges, T.	1983	The clinical value of negative temporal artery biopsy specimens
	Sorensen, P.	1977	Giant-cell arteritis, temporal arteritis and polymyalgia rheumatica. A retrospective study of 63 patients
	Ray B	2019	Diagnostic performance of (18)F-FDG PET-CT for large vessel involvement assessment in patients with suspected giant cell arteritis and negative temporal artery biopsy

- Studies reviewed and excluded:

Author	**Year**	**Title**	**Comments**

P. C. Grayson	2012	Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis	EXCLUDE: Describes LV involvement arteriography findings vs physical exam, but not TAB
J. C. Henes	2011	Cyclophosphamide for large vessel vasculitis: assessment of response by PET/CT	EXCLUDE: only includes 6 GCA patients
A. Brack	1999	Disease pattern in cranial and large-vessel giant cell arteritis	Exclude: Does not answer PICO
T. R. Skaug	1995	Clinical usefulness of biopsy in giant cell arteritis	Exclude: Does not answer PICO
S. E. Gabriel	1995	The use of clinical characteristics to predict the results of temporal artery biopsy among patients with suspected giant cell arteritis	Exclude: Does not answer PICO
G. P. Brittain	1991	Plasma viscosity or erythrocyte sedimentation rate in the diagnosis of giant cell arteritis?	Exclude: Does not answer PICO
R. B. Kent	1990	Temporal artery biopsy	Exclude: Does not answer PICO
N. D. Karanjia	1989	Too few, too late. Temporal artery biopsy in cranial arteritis	Exclude: Does not answer PICO and only 8 negative TAB patients
R. A. Stuart	1989	Temporary artery biopsy in suspected temporal arteritis: a five year survey	Exclude: does not answer PICO
J. Vilaseca	1987	Clinical usefulness of temporal artery biopsy	Exclude: Test accuracy for clinical sx's vs TAB
A. M. Roth	1984	The ultimate diagnoses of patients undergoing temporal artery biopsies	Exclude: Group 2 with 11 pts had neg TAB but still dx'd with GCA. Did not discuss outcomes of this group but looked at predictive factors (myalgias/PMR)
B. E. Malmvall	1980	The clinical pictures of giant cell arteritis. Temporal arteritis, polymyalgia rheumatica, and fever of unknown origin	Exclude: does not answer PICO

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 8:** In patients with suspected GCA what is impact of diagnostic confirmation by temporal artery biopsy versus clinical diagnosis alone on sustaining a diagnosis of GCA after one year of management and tissue biopsy-related adverse events?

- **Critical Outcomes:** Disease activity, clinical symptoms, damage from disease, pain, scarring, injury to tissue biopsied.

23. In patients with suspected GCA what is impact of diagnostic confirmation by temporal artery biopsy versus clinical diagnosis alone on sustaining a diagnosis of GCA after one year of management and tissue biopsy-related adverse events?
    - No comparative data available

24. In patients with suspected GCA what is impact of diagnostic confirmation by temporal artery biopsy on sustaining a diagnosis of GCA after one year of management and tissue biopsy-related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Symptoms at first and second TAB (the frequency of symptoms at TAB at 1 year was similar to the frequency at initial TAB)	Maleszewski, 2017	Prospective case-series	12 months	40 patients with GCA at start. Final cohort totals were: 3 months (n=10); 6 months (n=12); 9 months (n=9); 12 months (n=9)	First and second TABs with 12 months apart. Treatment after first TAB included high daily dose prednisone, median dose 60 mg/day (range 30-80mg/day), gradually reduced by an average of 10% of the daily dose every two weeks.	Headache: 28 patients at the beginning (70%), 12-month follow-up cohort 4/9 (44%) Jaw Claudication: 26 patients at the beginning (65%), 12-month follow-up cohort 4/9 (44%) Scalp Tenderness: 18 patients at the beginning (45%), 12-month follow-up cohort 5/9 (55%) Ischemic Optic Neuropathy: 6 patients at the beginning (15%), 12-month follow-up cohort 1/9 (11%) Systemic Symptoms: 19 patients at the beginning (48%), 12-month follow-up cohort 6/9 (67%) PMR: 15 patients at the beginning (38%), 12-month follow-up cohort 2/9 (22%)	

- **Test Accuracy results:**

Sensitivity	0.84 (95% CI: 0.72 to 0.92)
Specificity	0.99 (95% CI: 0.91 to 1.00)

Prevalence	40%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 40%	
True positives (patients with Giant Cell arteritis)	1 studies 54 patients	case-control type accuracy study	serious [a]	serious [b]	not serious	serious [c]	none	338 (290 to 368)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having Giant Cell arteritis)								62 (32 to 110)	
True negatives (patients without Giant Cell arteritis)	1 studies 80 patients	case-control type accuracy study	serious [a]	serious [b]	not serious	not serious	none	596 (545 to 600)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having Giant Cell arteritis)								4 (0 to 55)	

Explanations

a. Bias in patients selection: case-control design not avoided
b. The reference test was done at 70 months, giving indirectness in answering the PICO
c. pooled sensitivity has a broad confidence interval. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

25. In patients with suspected GCA what is impact of clinical diagnosis alone on sustaining a diagnosis of GCA after one year of management and tissue biopsy-related adverse events?

No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies :

Author	Year	Title
Maleszewski	2017	Clinical and pathological evolution of giant cell arteritis: a prospective study of follow-up temporal artery biopsies in 40 treated patients
Hall	1983	The therapeutic impact of temporal artery biopsy

- Studies reviewed and excluded:

Author	Year	Title	Comments
K. Bowling	2017	Temporal artery biopsy in the diagnosis of giant cell arteritis: Does the end justify the means?	Not enough data. Exclude
O. Hussain	2016	Diagnosis of giant cell arteritis: when should we biopsy the temporal artery?	Not enough data. Exclude
K. Le	2015	The effect of temporal artery biopsy on the treatment of temporal arteritis	Doesn't have one-year management timeline. Exclude
P. C. Grayson	2012	Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis	No biopsies done, no management/treatments described. Exclude
A. Cetinkaya	2008	Intraoperative predictability of temporal artery biopsy results	Doesn't have one-year management timeline. Compares surgeon's impression of arteries at dissection with TAB results. Exclude
B. Peral-Cagigal	2018	Temporal headache and jaw claudication may be the key for the diagnosis of giant cell arteritis	Not enough data. Doesn't have one-year management timeline. Exclude
V. Yuksel	2017	Clinical correlation of biopsy results in patients with temporal arteritis	Not enough data. Doesn't have one-year management timeline. Exclude
J. G. Jones	1981	Prognosis and management of polymyalgia rheumatica	PMR population.
L. F. Layfer	1978	Temporal arteriography. Analysis of 21 cases and a review of the literature	PMR population.
S. Sorensen	1977	Giant-cell arteritis, temporal arteritis and polymyalgia rheumatica. A retrospective study of 63 patients	TA and PMR population.

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 9:** In patients with GCA, what is the impact of routine monitoring (such as every 6-12 months) with non-invasive vascular imaging versus not performing routine monitoring with non-invasive vascular imaging on disease-related outcomes and diagnostic testing-related adverse events?

- **Critical Outcomes:** Disease activity, clinical symptoms, damage from disease (e.g., Ischemia limbs), relapse, death, adverse reaction to contrast exposure including nephrotoxicity (e.g., Gadolinium or CT contrast).

1. In patients with GCA, what is the impact of routine monitoring (such as every 6-12 months) with non-invasive vascular imaging versus not performing routine monitoring with non-invasive vascular imaging on disease-related outcomes and diagnostic testing-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	routine monitoring (such as every 6-12 months) with non-invasive vascular imaging [intervention]	not performing routine monitoring with non-invasive vascular imaging	Relative (95% CI)	Absolute (95% CI)		
Number of patients with Relapse												
1	observational studies	not serious	not serious	not serious	very serious [a]	none	14/29 (48.3%)	4/6 (66.7%)	OR 0.47 (0.07 to 2.96)	**182 fewer per 1,000** (from 544 fewer to 189 more)	⨁◯◯◯ VERY LOW	
Death												
1	observational studies	not serious	not serious	not serious	very serious [a]	none	2/29 (6.9%)	1/6 (16.7%)	OR 0.37 (0.03 to 4.90)	**98 fewer per 1,000** (from 161 fewer to 328 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision

- **References:**

- Randomized controlled trials:

None

- Comparative observational studies:

Author	Year	Title
D. Blockmans	2006	Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients

Giant Cell Arteritis (GCA)

Imaging, laboratory tests, and monitoring

- **PICO question 10:** In patients with GCA in apparent remission off of immunosuppressive therapy what is the impact of long-term routine clinical monitoring (such as every 3-6 months) versus no routine clinical monitoring on disease-related outcomes?

- **Critical Outcomes:** Disease activity, relapse, death, damage from disease

26. In patients with GCA in apparent remission off of immunosuppressive therapy what is the impact of long-term routine clinical monitoring (such as every 3-6 months) versus no routine clinical monitoring on disease-related outcomes?
    - No data available

27. In patients with GCA in apparent remission off of immunosuppressive therapy what is the impact of long-term routine clinical monitoring (such as every 3-6 months) on disease-related outcomes?
    - *Patient important outcomes:*

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Angiographic changes (physical exam findings had a positive correlation with angiographic findings in patients with	Grayson, 2012	Cross sectional	NA	Both Takayasu (n=68) and GCA (n=32) meeting ACR criteria were included. North American Cohort.	No intervention.	Using multivariable analysis to determine the prevalence ratio between physical exam findings and angiographic abnormalities: absent pulses 2.38 (1.69-3.38;p<0.001); bruits 1.51 (1.08-2.13;p=0.0174); ≥ 15mmHg difference in BP 1.18(0.86-1.63;p=0.3133)	Included Takayasu's patients as well. Not able to get pertinent information on exclusively GCA patients. Study does not directly address the PICO question.

GCA (32) and Takayasu (68)							

28. In patients with GCA in apparent remission off of immunosuppressive therapy what is the impact of no routine clinical monitoring on disease-related outcomes?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Grayson	2012	Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 11:** In patients with newly diagnosed GCA without manifestations of cranial ischemia, what is the impact of pulse IV glucocorticoids versus high dose oral glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, serious adverse events, infection, toxicity.

29. In patients with newly diagnosed GCA without manifestations of cranial ischemia, what is the impact of pulse IV glucocorticoids versus high dose oral glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

30.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse IV Glucocorticoids	High Dose Oral Glucocorticoids	Relative (95% CI)	Absolute (95% CI)	
Infections											
1 [1]	randomised trials	serious [1,a]	not serious	not serious	serious [b]	none	10/50 (20.0%)	6/53 (11.3%)	OR 1.77 (0.69 to 4.50)	**71 more per 1,000** (from 32 fewer to 252 more)	⊕⊕◯◯ LOW
Death											
1 [1]	randomised trials	serious [1,a]	not serious	not serious	very serious [b]	none	3/50 (6.0%)	0/53 (0.0%)	OR 7.41 (0.39 to 139.97)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW
Remission at week 36											
1 [2]	randomised trials	not serious	not serious	serious [2,c]	very serious [b]	none	10/14 (71.4%)	2/13 (15.4%)	OR 13.75 (2.05 to 92.04)	**560 more per 1,000** (from 118 more to 790 more)	⊕◯◯◯ VERY LOW
Remission at week 52											
1 [2]	randomised trials	not serious	not serious	serious [2,c]	very serious [b]	none	11/14 (78.6%)	2/13 (15.4%)	OR 20.17 (2.80 to 145.30)	**632 more per 1,000** (from 184 more to 810 more)	⊕◯◯◯ VERY LOW
Remission at week 78											
1 [2]	randomised trials	not serious	not serious	serious [2,c]	very serious [b]	none	12/14 (85.7%)	4/12 (33.3%)	OR 12.00 (1.76 to 81.74)	**524 more per 1,000** (from 135 more to 643 more)	⊕◯◯◯ VERY LOW
Relapses											
1 [2]	randomised trials	not serious	not serious	serious [2,c]	serious [b]	none	14/21 (66.7%)	13/37 (35.1%)	OR 3.69 (1.19 to 11.44)	**315 more per 1,000** (from 41 more to 510 more)	⊕⊕◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Allocation concealment not mentioned; No blinding of participants; No blinding of personnel; No blinding of outcome assessment.
b. Treatment would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision.
c. RCT of IV methylprednisolone or IV saline for 3 consecutive days. Also, all patients were started on 40 mg/day prednisone and followed the same tapering schedule as long as disease activity was controlled.

References

1. Chevalet, . 2000.
2. Mazlumzadeh, . . 2006.

- **References:**

- Randomized controlled trials:

Author	Year	Title
Chevalet, P	2000	A randomized, multicenter, controlled trial using intravenous pulses of methylprednisolone in the initial treatment of simple forms of giant cell arteritis: a one year follow up study of 164 patients
Mazlumzadeh, M	2006	Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 11:** In patients with newly diagnosed GCA without manifestations of cranial ischemia, what is the impact of pulse IV glucocorticoids versus high dose oral glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, serious adverse events, infection, toxicity.

31. In patients with newly diagnosed GCA without manifestations of cranial ischemia, what is the impact of pulse IV glucocorticoids versus high dose oral glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

32.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse IV Glucocorticoids	High Dose Oral Glucocorticoids	Relative (95% CI)	Absolute (95% CI)	
Infections											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse IV Glucocorticoids	High Dose Oral Glucocorticoids	Relative (95% CI)	Absolute (95% CI)	
1 [1]	randomised trials	serious [1,a]	not serious	not serious	serious [b]	none	10/50 (20.0%)	6/53 (11.3%)	OR 1.77 (0.69 to 4.50)	**71 more per 1,000** (from 32 fewer to 252 more)	⨁⨁◯◯ LOW
Death											
1 [1]	randomised trials	serious [1,a]	not serious	not serious	very serious [b]	none	3/50 (6.0%)	0/53 (0.0%)	OR 7.41 (0.39 to 139.97)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW
Remission at week 36											
1 [2]	randomised trials	not serious	not serious	serious [2,c]	very serious [b]	none	10/14 (71.4%)	2/13 (15.4%)	OR 13.75 (2.05 to 92.04)	**560 more per 1,000** (from 118 more to 790 more)	⨁◯◯◯ VERY LOW
Remission at week 52											
1 [2]	randomised trials	not serious	not serious	serious [2,c]	very serious [b]	none	11/14 (78.6%)	2/13 (15.4%)	OR 20.17 (2.80 to 145.30)	**632 more per 1,000** (from 184 more to 810 more)	⨁◯◯◯ VERY LOW
Remission at week 78											
1 [2]	randomised trials	not serious	not serious	serious [2,c]	very serious [b]	none	12/14 (85.7%)	4/12 (33.3%)	OR 12.00 (1.76 to 81.74)	**524 more per 1,000** (from 135 more to 643 more)	⨁◯◯◯ VERY LOW
Relapses											
1 [2]	randomised trials	not serious	not serious	serious [2,c]	serious [b]	none	14/21 (66.7%)	13/37 (35.1%)	OR 3.69 (1.19 to 11.44)	**315 more per 1,000** (from 41 more to 510 more)	⨁⨁◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Allocation concealment not mentioned; No blinding of participants; No blinding of personnel; No blinding of outcome assessment.

b. Treatment would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision.
c. RCT of IV methylprednisolone or IV saline for 3 consecutive days. Also, all patients were started on 40 mg/day prednisone and followed the same tapering schedule as long as disease activity was controlled.

References

1. Chevalet, 2000.
2. Mazlumzadeh, 2006.

- **References:**

- Randomized controlled trials:

Author	Year	Title
Chevalet, P	2000	A randomized, multicenter, controlled trial using intravenous pulses of methylprednisolone in the initial treatment of simple forms of giant cell arteritis: a one year follow up study of 164 patients
Mazlumzadeh, M	2006	Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 13:** In patients with newly diagnosed GCA, what is the impact of using daily aspirin (81 to 325 mg) versus not using aspirin on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Clinical symptoms, disease related damage, death, serious adverse events (e.g., bleeding), toxicity leading to discontinuation.

33. In In patients with newly diagnosed GCA, what is the impact of using daily aspirin (81 to 325 mg) versus not using aspirin on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	No Antiplatelet Therapy	Relative (95% CI)	Absolute (95% CI)	
Relapse (no. of patients)											
1 [1]	observational studies	not serious	not serious	not serious	not serious	none	18/37 (48.6%)	48/84 (57.1%)	OR 0.71 (0.33 to 1.54)	**85 fewer per 1,000** (from 266 fewer to 101 more)	⨁⨁◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	No Antiplatelet Therapy	Relative (95% CI)	Absolute (95% CI)	
Severe Ischemic Complications at Presentation (no. of patients)											
2 [1,2]	observational studies	not serious	not serious	not serious	not serious	none	12/73 (16.4%)	65/223 (29.1%)	OR 0.45 (0.13 to 1.48)	**135 fewer per 1,000** (from 241 fewer to 87 more)	⨁⨁◯◯ LOW
Cumulative Prednisone Dose (g)											
1 [1]	observational studies	not serious	not serious	not serious	not serious	none	37	84	-	MD **1.7 lower** (3.98 lower to 0.58 higher)	⨁⨁◯◯ LOW
Duration of Therapy											
1 [1]	observational studies	not serious	not serious	not serious	not serious	none	37	84	-	MD **3.8 lower** (13.06 lower to 5.46 higher)	⨁⨁◯◯ LOW
Severe Ischemic Complications on Follow-up (no. of patients)											
1 [2]	observational studies	not serious	not serious	not serious	not serious	none	2/73 (2.7%)	12/93 (12.9%)	OR 0.19 (0.04 to 0.88)	**102 fewer per 1,000** (from 123 fewer to 14 fewer)	⨁⨁◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

References

1. Narvaez, 2008.
2. Nesher, 2004.

- **References:**

- Randomized controlled trials:

- None

- Comparative observational studies:

Author	Year	Title
Narvaez, J	2008	Impact of antiplatelet therapy in the development of severe ischemic complications and in the outcome of patients with giant cell arteritis
Nesher, G	2004	Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 14:** In patients with newly diagnosed GCA without cranial ischemic manifestations, what is the impact of initial high dose oral glucocorticoids versus moderate dose oral glucocorticoids on disease-related outcomes, cumulative glucocorticoid dose, and treatment-related adverse events?

- **Critical Outcomes:** Activity of Disease, Clinical Symptoms, Disease Related Damage, Relapse, Serious Adverse Events, Infection, Toxicity.

34. In patients with newly diagnosed GCA without cranial ischemic manifestations, what is the impact of initial high dose oral glucocorticoids versus moderate dose oral glucocorticoids on disease-related outcomes, cumulative glucocorticoid dose, and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderate Dose	High Dose Glucocorticoids	Relative (95% CI)	Absolute (95% CI)	
Relapses (no of patients)											
3 [1,2,3]	observational studies	not serious	not serious	not serious	serious	none	43/129 (33.3%)	40/129 (31.0%)	OR 1.06 (0.55 to 2.04)	**13 more per 1,000** (from 112 fewer to 168 more)	⊕◯◯◯ VERY LOW
Death											
1 [3]	observational studies	not serious	not serious	not serious	serious	none	1/53 (1.9%)	3/50 (6.0%)	OR 0.30 (0.03 to 3.00)	**41 fewer per 1,000** (from 58 fewer to 101 more)	⊕◯◯◯ VERY LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderate Dose	High Dose Glucocorticoids	Relative (95% CI)	Absolute (95% CI)	
GC-related Adverse Events (no of patients)											
3 [1,2,3]	observational studies	not serious	not serious	not serious	not serious	none	50/129 (38.8%)	97/129 (75.2%)	OR 0.19 (0.07 to 0.48)	**386 fewer per 1,000** (from 577 fewer to 159 fewer)	⊕⊕◯◯ LOW
Infections (Serious)											
1 [3]	observational studies	serious [3,a]	not serious	not serious	serious	none	6/53 (11.3%)	3/50 (6.0%)	OR 2.00 (0.47 to 8.47)	**53 more per 1,000** (from 31 fewer to 291 more)	⊕◯◯◯ VERY LOW
GCA-related complications											
2 [1,3]	observational studies	not serious	not serious	not serious	serious	none	8/106 (7.5%)	12/75 (16.0%)	OR 0.46 (0.15 to 1.35)	**79 fewer per 1,000** (from 132 fewer to 45 more)	⊕◯◯◯ VERY LOW
Serious GC related Side Effects											
1 [2]	observational studies	not serious	not serious	not serious	not serious	none	5/23 (21.7%)	33/54 (61.1%)	OR 0.18 (0.06 to 0.55)	**391 fewer per 1,000** (from 525 fewer to 148 fewer)	⊕⊕◯◯ LOW
Remission											
1 [1]	observational studies	serious [a]	not serious	not serious	serious	none	29/53 (54.7%)	11/25 (44.0%)	OR 1.54 (0.59 to 4.01)	**108 more per 1,000** (from 123 fewer to 319 more)	⊕◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Not explicit that these are newly diagnosed

References

1. Delecoeuillerie, 1988.
2. Nesher, 1997.
3. Les, 2015.

- **References:**

- Randomized controlled trials:
  - None
- Comparative observational studies:

Author	Year	Title
Les, I	2015	Effectiveness and safety of medium-dose prednisone in giant cell arteritis: a retrospective cohort study of 103 patients
Nesher, G	1997	Efficacy and adverse effects of different corticosteroid dose regimens in temporal arteritis: a retrospective study
Delecoeullerie, G	1988	Polymyalgia rheumatica and temporal arteritis: a retrospective analysis of prognostic features and different corticosteroid regimens (11 year survey of 210 patients)

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 15:** In patients with newly diagnosed GCA, what is the impact of oral glucocorticoids with non-glucocorticoid immunosuppressive therapy versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, Disease Related Damage, Relapse, Serious Adverse Events, Infection, Toxicity, Malignancy, Death

35. In patients with newly diagnosed GCA, what is the impact of oral glucocorticoids with non-glucocorticoid immunosuppressive therapy versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral glucocorticoids w/ non-glucocorticoid immunosuppressive therapy	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)	
Relapse at 1 year											
7 [1,2,3,4,5,6,7,8,a]	randomised trials	not serious	not serious	not serious	not serious [b]	none	91/166 (54.8%)	102/156 (65.4%)	OR 0.87 (0.73 to 1.04)	**32 fewer per 1,000** (from 74 fewer to 9 more)	⊕⊕⊕⊕ HIGH
SAE											
6 [2,3,4,7,9,10]	randomised trials	not serious	not serious	not serious	serious [b]	none	40/152 (26.3%)	48/141 (34.0%)	OR 0.81 (0.54 to 1.20)	**46 fewer per 1,000** (from 122 fewer to 42 more)	⊕⊕⊕◯ MODERATE
Infections											
7 [1,2,3,5,7,9,10]	randomised trials	not serious	not serious	serious	serious [b]	none	104/164 (63.4%)	77/148 (52.0%)	OR 1.25 (0.87 to 1.79)	**55 more per 1,000** (from 35 fewer to 140 more)	⊕⊕◯◯ LOW
Serious infections											
4 [3,6,7,9]	randomised trials	not serious	not serious	not serious	serious [b]	none	9/155 (5.8%)	13/148 (8.8%)	OR 0.69 (0.29 to 1.64)	**26 fewer per 1,000** (from 61 fewer to 49 more)	⊕⊕⊕◯ MODERATE
Relapses during the 3 month follow-up phase (15 months)											
1 [2]	randomised trials	not serious	not serious	not serious	not serious	none	2/8 (25.0%)	9/9 (100.0%)	RR 0.29 (0.10 to 0.85)	**710 fewer per 1,000** (from 900 fewer to 150 fewer)	⊕⊕⊕⊕ HIGH
Malignancy											
2 [1,3]	randomised trials	not serious	not serious	not serious	very serious [b]	none	2/40 (5.0%)	2/25 (8.0%)	OR 0.74 (0.11 to 4.99)	**20 fewer per 1,000** (from 71 fewer to 223 more)	⊕⊕◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral glucocorticoids w/ non-glucocorticoid immunosuppressive therapy	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)	
Relapse at 48 weeks (Leflunomide + GC)											
1 [11,c]	observational studies	not serious	not serious	not serious	not serious	none	4/30 (13.3%)	18/46 (39.1%)	OR 0.24 (0.07 to 0.80)	**258 fewer per 1,000** (from 348 fewer to 52 fewer)	⨁⨁◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

Explanations

a. Koster, 2001. This case control study provides data about relapse that can't be pooled with the other studies, but provides similar results. RR comparing relapse rates before and after MTX initiation/index date were significantly reduced in both cases (RR 0.32, 95% CI 0.24–0.41) and controls (RR 0.60, 95% CI 0.43–0.86). The decrease in relapse rate was significantly greater in patients taking MTX than in those taking GC alone (p = 0.004)
b. Wide CI might cross clinical decision threshold that dictates recommending versus not recommending Oral glucocorticoids with non-glucocorticoid immunosuppressive therapy.
c. Open-Label Study

References

1. Spiera, R. 2001.
2. Martinez, T. 2007.
3. Hoffman, G. 2007.
4. Langford, C. 2007.
5. Jover, J. 2001.
6. Hoffman, G. 2002.
7. Seror, 2014.
8. Koster, 2001.
9. Stone, 2017.
10. Villiger, 2016.
11. Hocevar, 2019.

- **References:**

- Randomized controlled trials:

Author	Year	Title

Spiera, R	2001	A prospective, double-blind, randomized, placebo-controlled trial of methotrexate in the treatment of giant cell arteritis
Martinez, T	2007	A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica
Hoffman, G	2007	Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial
Jover, J	2001	Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial
Hoffman, G	2002	A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis
Serror, R	2014	Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial
Stone	2017	Trial of Tocilizumab in Giant-Cell Arteritis
Villger	2016	Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial
Alojzija Hočevar	2019	Does leflunomide have a role in giant cell arteritis? An open-label study
Matthew J. Koster	2001	Efficacy of Methotrexate in Real-world Management of Giant Cell Arteritis: A Case-control Study. The Journal of Rheumatology May 2019, 46 (5) 501-508; DOI: https://doi.org/10.3899/jrheum.180429

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 16:** In patients with newly diagnosed GCA, what is the impact of oral glucocorticoids with tocilizumab versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, death, serious adverse events (e.g., bowel perforation), infection, toxicity.

36. In patients with newly diagnosed GCA, what is the impact of oral glucocorticoids with tocilizumab versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Weekly Tocilizumab:**

- Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral glucocorticoids with tocilizumab	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
SF-36 PCS, weekly TCZ at 52 weeks (assessed with: higher scores representing better function; Scale from: 0 to 100)												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	100	50	-	MD **4.38 higher** (1.58 lower to 10.34 higher)	⨁⨁◯◯ LOW	
SF-36 MCS, weekly TCZ at 52 weeks (assessed with: higher scores representing better function; Scale from: 0 to 100)												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	100	50	-	MD **0.61 higher** (5.86 lower to 7.08 higher)	⨁⨁◯◯ LOW	
VAS weekly TCZ at 52 week (assessed with: higher scores indicating greater disease activity; Scale from: 0 to 100)												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	100	50	-	MD **15.6 lower** (34.3 lower to 3.1 higher)	⨁⨁◯◯ LOW	
First relapse												
1 [c]	randomised trials	not serious	not serious	not serious	serious [b]	none	1/20 (5.0%)	5/10 (50.0%)	**RR 0.10** (0.01 to 0.75)	**450 fewer per 1,000** (from 495 fewer to 125 fewer)	⨁⨁⨁◯ MODERATE	
SAE, weekly TCZ, 52 week												
2 [a,c]	randomised trials	not serious	not serious	not serious	very serious [b]	none	22/120 (18.3%)	16/60 (26.7%)	**RR 0.69** (0.40 to 1.19)	**83 fewer per 1,000** (from 160 fewer to 51 more)	⨁⨁◯◯ LOW	
Serious Infections, weekly TCZ, 52 weeks												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	7/100 (7.0%)	2/50 (4.0%)	**RR 1.75** (0.38 to 8.12)	**30 more per 1,000** (from 25 fewer to 285 more)	⨁⨁◯◯ LOW	
Remission at 52 weeks, weekly TCZ												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	56/100 (56.0%)	7/50 (14.0%)	**RR 4.00** (1.97 to 8.12)	**420 more per 1,000** (from 136 more to 997 more)	⨁⨁◯◯ LOW	
Flares, weekly TCZ												

- Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral glucocorticoids with tocilizumab	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
1 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none	23/100 (23.0%)	34/50 (68.0%)	**RR 0.34** (0.23 to 0.51)	**449 fewer per 1,000** (from 524 fewer to 333 fewer)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. J. H. Stone, 2017, "Trial of Tocilizumab in Giant-Cell Arteritis"
b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth
c. P. M. Villiger, 2016, "Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomized, double-blind, placebo-controlled trial"

- Bi-weekly Tocilizumab:

- Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral glucocorticoids with tocilizumab	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
SF-36 PCS, bi-weekly TCZ at 52 weeks (assessed with: higher scores representing better function; Scale from: 0 to 100)												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	49	50	-	MD **3.04 higher** (3.43 lower to 9.51 higher)	⨁⨁◯◯ LOW	
SF-36 MCS, bi-weekly TCZ at 52 weeks (assessed with: higher scores representing better function; Scale from: 0 to 100)												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	49	50	-	MD **0.56 lower** (7.64 lower to 6.52 higher)	⨁⨁◯◯ LOW	
VAS bi-weekly TCZ at 52 week (assessed with: higher scores indicating greater disease activity; Scale from: 0 to 100)												
1 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none	49	50	-	MD **21.9 lower** (42.4 lower to 1.4 lower)	⨁⨁⨁◯ MODERATE	
SAE, bi-weekly TCZ, 52 week												

- Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral glucocorticoids with tocilizumab	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	7/49 (14.3%)	11/50 (22.0%)	**RR 0.65** (0.27 to 1.54)	**77 fewer per 1,000** (from 161 fewer to 119 more)	⨁⨁◯◯ LOW	
Serious Infections, bi-weekly TCZ, 52 weeks												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	2/49 (4.1%)	2/50 (4.0%)	**RR 1.02** (0.15 to 6.96)	**1 more per 1,000** (from 34 fewer to 238 more)	⨁⨁◯◯ LOW	
Remission at 52 weeks, bi-weekly TCZ												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	26/49 (53.1%)	7/50 (14.0%)	**RR 3.79** (1.82 to 7.91)	**391 more per 1,000** (from 115 more to 967 more)	⨁⨁◯◯ LOW	
Flares, bi-weekly TCZ												
1 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none	13/49 (26.5%)	34/50 (68.0%)	**RR 0.39** (0.24 to 0.65)	**415 fewer per 1,000** (from 517 fewer to 238 fewer)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. J. H. Stone, 2017, "Trial of Tocilizumab in Giant-Cell Arteritis"
b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

Author	Year	Title
P. M. Villiger	2016	Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial
J. H. Stone	2017	Trial of Tocilizumab in Giant-Cell Arteritis

- Studies reviewed and excluded:

- The suggested *Stone, J. H., Tuckwell, K. , Dimonaco, S. , Klearman, M. , Aringer, M. , Blockmans, D. , Brouwer, E. , Cid, M. C., Dasgupta, B. , Rech, J. , Salvarani, C. , Schulze-Koops, H. , Schett, G. , Spiera, R. , Unizony, S. H. and Collinson, N. (2019), Glucocorticoid Doses and Acute-Phase Reactants at Giant Cell Arteritis Flare in a Randomized Trial of Tocilizumab. Arthritis Rheumatol. Accepted Author Manuscript. doi:10.1002/art.40876*, has the same data as Stone 2017, for which data was abstracted already.
- The suggested *Vibeke Strand et. al, Health-related quality of life in patients with giant cell arteritis treated with tocilizumab in a phase 3 randomised controlled trial. Arthritis Research & Therapy. 2019;21(1):1-9 DOI 10.1186/s13075-019-1837-7*, has the same data as Stone 2017, for which data was abstracted already.

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 17:** In patients with newly diagnosed GCA, what is the impact of oral glucocorticoids with abatacept versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, death, serious adverse events, infection, toxicity.

37. In patients with newly diagnosed GCA, what is the impact of oral glucocorticoids with abatacept versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

38. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral glucocorticoids with abatacept	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
complete remission												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	10/20 (50.0%)	7/21 (33.3%)	OR 2.00 (0.57 to 7.06)	**167 more per 1,000** (from 112 fewer to 446 more)	⨁⨁◯◯ LOW	
serious adverse events												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	10/20 (50.0%)	8/21 (38.1%)	OR 1.63 (0.47 to 5.63)	**120 more per 1,000** (from 157 fewer to 395 more)	⨁⨁◯◯ LOW	
deaths												
1	randomised trials	not serious	not serious	not serious	not serious [a]	none	0/20 (0.0%)	0/21 (0.0%)	not estimable since no deaths happened in both groups			
relapses												

38. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral glucocorticoids with abatacept	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	10/20 (50.0%)	14/21 (66.7%)	OR 0.50 (0.14 to 1.77)	**167 fewer per 1,000** (from 448 fewer to 113 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

Author	Year	Title
C. A. Langford,	2017	A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 18:** In patients with newly diagnosed GCA, what is the impact of alternate day oral glucocorticoids versus daily oral glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, serious adverse events, infection, toxicity.

39. In patients with newly diagnosed GCA, what is the impact of alternate day oral glucocorticoids versus daily oral glucocorticoids on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

40.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	alternate day oral glucocorticoids	daily oral glucocorticoids	Relative (95% CI)	Absolute (95% CI)		

remission at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	alternate day oral glucocorticoids	daily oral glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	6/20 (30.0%)	16/20 (80.0%)	OR 0.11 (0.03 to 0.46)	**494 fewer per 1,000** (from 693 fewer to 152 fewer)	⨁⨁◯◯ LOW	

Hypercortisonism at 4 weeks

1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	2/20 (10.0%)	7/20 (35.0%)	OR 0.21 (0.04 to 1.16)	**248 fewer per 1,000** (from 329 fewer to 34 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Blinding of participants and personnel (performance bias) not done, blinding of outcome assessment (detection bias) not done
b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

Author	Year	Title
G. G. Hunder	1975	Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 19:** In patients with newly diagnosed GCA, what is the impact of statin use versus not using a statin on cardiovascular events, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Disease related damage, death, patient reported outcomes, serious adverse events, toxicity.

41. In patients with newly diagnosed GCA, what is the impact of statin use versus not using a statin on cardiovascular events, disease-related outcomes, and treatment-related adverse events?

42. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statin	not using Statin	Relative (95% CI)	Absolute (95% CI)		
Visual manifestations												
2 [a]	observational studies	not serious	serious [b]	not serious	very serious [c]	none	11/47 (23.4%)	28/128 (21.9%)	OR 1.03 (0.47 to 2.25)	**5 more per 1,000** (from 102 fewer to 168 more)	⨁◯◯◯ VERY LOW	
Fever												
2 [a]	observational studies	not serious	not serious	not serious	very serious [c]	none	8/47 (17.0%)	20/128 (15.6%)	OR 0.97 (0.37 to 2.51)	**4 fewer per 1,000** (from 92 fewer to 161 more)	⨁◯◯◯ VERY LOW	
Headache												
2 [a]	observational studies	not serious	not serious	not serious	very serious [c]	none	43/47 (91.5%)	116/128 (90.6%)	OR 1.17 (0.35 to 3.85)	**13 more per 1,000** (from 134 fewer to 68 more)	⨁◯◯◯ VERY LOW	
Relapse first year [e]												
2 [a]	observational studies	not serious	not serious	not serious	very serious [c]	none	23/47 (48.9%)	52/128 (40.6%)	OR 1.71 (0.81 to 3.59)	**133 more per 1,000** (from 50 fewer to 304 more)	⨁◯◯◯ VERY LOW	
Cardiovascular hospitalization												
1 [d]	observational studies	not serious	not serious	not serious	serious [c]	none	0/28 (0.0%)	18/75 (24.0%)	OR 0.06 (0.01 to 1.01)	**221 fewer per 1,000** (from 237 fewer to 2 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Narvaez, 2007 and Garcia, 2004
b. The effect estimate (OR) in Narvaez,2007 does not meet with the confidence interval of the OR in Garcia, 2004
c. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth
d. Pugnet, 2016
e. Shmidt, 2013 could not be pooled but had consistent results, it showed that while not statistically significant, statin users may be more likely to experience a first relapse (HR: 1.40; 95% CI: 0.96, 2.03; p=0.07).

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

Author	Year	Title
J. Narvaez	2007	Statin therapy does not seem to benefit giant cell arteritis
A. Garcia-Martinez	2004	Treatment with statins does not exhibit a clinically relevant corticosteroid-sparing effect in patients with giant cell arteritis
G. Pugnet	2016	Predictors of Cardiovascular Hospitalization in Giant Cell Arteritis: Effect of Statin Exposure. A French Population-based Study.
J. Schmidt	2013	Statin Use in Giant Cell Arteritis: A Retrospective Study. https://doi.org/10.3899/jrheum.121150

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 20:** In patients with GCA on glucocorticoids, what is the impact of tapering glucocorticoids off by 6 months versus tapering glucocorticoids off over a period longer than 6 months on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, patient reported outcomes, death, serious adverse events, infection, toxicity.

43. In patients with GCA on glucocorticoids, what is the impact of tapering glucocorticoids off by 6 months versus tapering glucocorticoids off over a period longer than 6 months on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tapering glucocorticoids off by 6 months	tapering glucocorticoids off over a period longer than 6 months	Relative (95% CI)	Absolute (95% CI)		
Remission												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	7/50 (14.0%)	9/51 (17.6%)	RR 0.79 (0.32 to 1.97)	**37 fewer per 1,000** (from 120 fewer to 171 more)	⨁⨁◯◯ LOW	
Flares												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	34/50 (68.0%)	25/51 (49.0%)	RR 1.39 (0.99 to 1.95)	**191 more per 1,000** (from 5 fewer to 466 more)	⨁⨁⨁◯ MODERATE	
Serious adverse events 52 week												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	11/50 (22.0%)	13/51 (25.5%)	RR 0.86 (0.43 to 1.74)	**36 fewer per 1,000** (from 145 fewer to 189 more)	⨁⨁◯◯ LOW	
Serious Infections, 52 weeks												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/50 (4.0%)	6/51 (11.8%)	RR 0.34 (0.07 to 1.61)	**78 fewer per 1,000** (from 109 fewer to 72 more)	⨁⨁◯◯ LOW	
Any Infection, 52 weeks												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	38/50 (76.0%)	33/51 (64.7%)	RR 1.17 (0.91 to 1.52)	**110 more per 1,000** (from 58 fewer to 336 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

Author	Year	Title
J. H. Stone	2017	Trial of Tocilizumab in Giant-Cell Arteritis

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 21:** In patients with GCA with extra-cranial large vessel involvement, what is the impact of oral glucocorticoids with a non-glucocorticoid immunosuppressive agent versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, serious adverse events, infection, malignancy, toxicity.

44. In patients with GCA with extra-cranial large vessel involvement, what is the impact of oral glucocorticoids with a non-glucocorticoid immunosuppressive agent versus oral glucocorticoids alone on cumulative glucocorticoid dose, disease-related outcomes, and treatment-related adverse events?

45. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral glucocorticoids with a non-glucocorticoid immunosuppressive agen	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
Relapse at 1 year												
3 [a,b,c]	randomised trials	not serious	serious [d]	serious [e]	serious [f]	none	60/98 (61.2%)	73/101 (72.3%)	RR 0.84 (0.62 to 1.14)	**116 fewer per 1,000** (from 275 fewer to 101 more)	⨁◯◯◯ VERY LOW	
SAE												
1 [a]	randomised trials	not serious	not serious	serious [e]	serious [f]	none	5/27 (18.5%)	17/35 (48.6%)	RR 0.38 (0.16 to 0.90)	**301 fewer per 1,000** (from 408 fewer to 49 fewer)	⨁⨁◯◯ LOW	
Infections												

45. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral glucocorticoids with a non-glucocorticoid immunosuppressive agen	oral glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
2 [a,c]	randomised trials	not serious	serious [g]	serious [e]	serious [f]	none	28/47 (59.6%)	21/54 (38.9%)	RR 1.37 (0.45 to 4.14)	**144 more per 1,000** (from 214 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	
Serious infections												
2 [a,b]	randomised trials	not serious	not serious	serious [e]	serious [f]	none	4/78 (5.1%)	10/82 (12.2%)	RR 0.48 (0.16 to 1.43)	**63 fewer per 1,000** (from 102 fewer to 52 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Seror, 2014
b. Hoffman, 2002
c. Jover, 2001
d. The effect estimate (OR) in Jover, 2001 does not cross the confidence interval of the 2 other studies. the measure of heterogeneity I2= 55%.
e. It's not specified is all the GCA patients have extra-cranial large vessel involvement
f. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth
g. The effect estimates of the 2 included studies do not cross each other's confidence intervals. the measure of heterogeneity I2= 85%.

- **References:**

- Randomized controlled trials:

Author	Year	Title
R. Seror	2014	Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial
G. S. Hoffman	2002	A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis
J. A. Jover	2001	Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial

Giant Cell Arteritis (GCA)

Medical Treatment

- **PICO question 22:** In patients with GCA who are in remission off of glucocorticoids and on non-glucocorticoid immunosuppressive therapy for 1 year, what is the effect of discontinuing non-glucocorticoid immunosuppressive therapy versus continuing non-glucocorticoid immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, serious adverse events, infection, malignancy, toxicity, death.

46. In patients with GCA who are in remission off of glucocorticoids and on non-glucocorticoid immunosuppressive therapy for 1 year, what is the effect of discontinuing non-glucocorticoid immunosuppressive therapy versus continuing non-glucocorticoid immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?
    - No comparative data available

47. In patients with GCA who are in remission off of glucocorticoids and on non-glucocorticoid immunosuppressive therapy for 1 year, what is the effect of discontinuing non-glucocorticoid immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?
    - No single arm data available

48. In patients with GCA who are in remission off of glucocorticoids and on non-glucocorticoid immunosuppressive therapy for 1 year, what is the effect of continuing non-glucocorticoid immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?
    - No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

  None

Giant Cell Arteritis (GCA)

Medical treatment

- **PICO question 23:** In asymptomatic patients with GCA who have rising inflammatory markers, what is the impact of continued clinical observation without escalation of immunosuppression versus escalating immunosuppression on disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Activity of disease, Clinical symptoms, disease related damage, relapse, serious adverse events, infection, toxicity, death, malignancy

49. In asymptomatic patients with GCA who have rising inflammatory markers, what is the impact of continued clinical observation without escalation of immunosuppression versus escalating immunosuppression on disease-related outcomes, and treatment-related adverse events?
    - No comparative data available

50. In asymptomatic patients with GCA who have rising inflammatory markers, what is the impact of continued clinical observation without escalation of immunosuppression on disease-related outcomes, and treatment-related adverse events?
    - No single arm data available

51. In asymptomatic patients with GCA who have rising inflammatory markers, what is the impact of escalating immunosuppression on disease-related outcomes, and treatment-related adverse events?
    - No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

  None

Giant Cell Arteritis (GCA)

Surgical Intervention

- **PICO question 24:** In patients with GCA with severe disease, what is the impact of surgical intervention with immunosuppression versus immunosuppression alone on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?

- **Critical Outcomes:** Damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation, ischemic events, complications of the intervention such as bleeding or thrombotic events, need for additional intervention, death

52. In patients with GCA with severe disease, what is the impact of surgical intervention with immunosuppression versus immunosuppression alone on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
    - No comparative data available

53. In patients with GCA with severe disease, what is the impact of surgical intervention with immunosuppression on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease-related outcomes	Both, 2006	Observational, single arm	Mean 24 m (range 5-101)	10 GCA patients with symptomatic large artery involvement undergoing PTA of upper extremity arterial lesion. 9/10 meet ACR criteria. Germany. 1995-2004.	Percutaneous transluminal angioplasty	Immediate technical success rate of 100%. Cumulative primary patency rate 65.2% (SE 8.9%). Repeat angioplasty with cumulative secondary patency rate of 82.6% (SE 7.1%). Cumulative tertiary patency rate of 89.7% (SE 5.6%). 5/10 patients without clinical signs of relapsing stenosis	1 patient did not fulfill ACR criteria but had bilateral UE arm manifestations and PMR.
Surgical intervention -related adverse events	Both, 2006	Observational, single arm	Mean 24 m (range 5-101)	10 GCA patients with symptomatic large artery involvement undergoing PTA of upper extremity arterial lesion. 9/10 meet ACR criteria. Germany. 1995-2004.	Percutaneous transluminal angioplasty	Hematoma at puncture site in 1/10 patients. Iatrogenic femoral artery pseudoaneurysm in 1/10 patients.	1 patient did not fulfill ACR criteria but had bilateral UE arm manifestations and PMR.

54. In patients with GCA with severe disease, what is the impact of immunosuppression alone on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?

No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies :

Author	Year	Title
Both	2006	Balloon angioplasty of arteries of the upper extremities in patients with extracranial giant-cell arteritis

Giant Cell Arteritis (GCA)

Surgical intervention

- **PICO question 25:** In patients with GCA and severe disease, what is the impact of performing surgical intervention while the patient has active disease versus delaying until the disease is in remission on disease-related outcomes and surgical intervention-related adverse events?

- **Critical Outcomes:** Damage from disease, disease activity, relapse, infection, ischemic events, complications of the intervention such as bleeding or thrombotic events, need for additional intervention, death.

55. In patients with GCA and severe disease, what is the impact of performing surgical intervention while the patient has active disease versus delaying until the disease is in remission on disease-related outcomes and surgical intervention-related adverse events?
    - No comparative data available

56. In patients with GCA and severe disease, what is the impact of performing surgical intervention while the patient has active disease on disease-related outcomes and surgical intervention-related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Operative Mortality	Mennander, 2008	Observational, retrospective	Mean f/u of 4 years	100 patients undergoing repair of ascending aortic aneurysm with histological evidence of GCA or lympho-plasmacytic aortitis (excluding Takayasu's, infective aoritis, mixed inflammatory dz or simple atherosclerosis.	Repair of ascending aortic aneurysm.	Operative mortality in 4/100 patients. Late death related to low output syndrome in 3/100	Cohort not limited to GCA but also patients with isolated aortitis. No mention of needing to meet (ACR) criteria for GCA.
Complications of intervention	Mennander, 2008	Observational, retrospective	Mean f/u of 4 years	100 patients undergoing repair of ascending aortic aneurysm with histological evidence of GCA or lympho-plasmacytic aortitis (excluding Takayasu's, infective aoritis, mixed inflammatory dz or simple atherosclerosis.	Repair of ascending aortic aneurysm.	Mediastinitis: 1/100 Stroke: 4/100 Myocardial infarction: 0/100 Low output syndrome 4/100 Renal insufficiency: 8/100 Reoperations for bleeding: 4/100	Cohort not limited to GCA but also patients with isolated aortitis. No mention of needing to meet (ACR) criteria for GCA.
Need for additional interventions (2 studies with 221 patients assessed the need for additional interventions, one study had 3/100 and another	Mennander, 2008	Observational, retrospective	Mean f/u of 4 years	100 patients undergoing repair of ascending aortic aneurysm with histological evidence of GCA or lympho-plasmacytic aortitis (excluding Takayasu's, infective aoritis, mixed inflammatory dz or simple atherosclerosis.	Repair of ascending aortic aneurysm.	2/100 required reoperation for aortic regurgitation. 1/100 required reoperation for coronary button pseudoaneurysm.	Cohort not limited to GCA but also patients with isolated aortitis. No mention of needing to meet (ACR) criteria for GCA.

had 48/121 patients, leading to high inconsistency)	Clifford AH, 2019	Observational retrospective cohort	Mean f/u 56.2 ± 45.4 mon	121 pts undergoing aortic root/ascending aorta or aortic arch repair at Cleveland Clinic with at least 6 month f/u data (29 GCA, 11 TAK, 73 CIA, 8 Other)	Aortic root/ascending aorta or aortic arch repair	48 pts out of 121 pts went on to require 74 additional vascular procedures.	Cohort not limited to GCA but include other forms of large vessel vasculitis including Takayasu's and clinically isolated aortitis (CIA).
Relapse	Clifford AH, 2019	Observational retrospective cohort	Mean f/u 56.2 ± 45.4 mon	121 pts undergoing aortic root/ascending aorta or aortic arch repair at Cleveland Clinic with at least 6 month f/u data (29 GCA, 11 TAK, 73 CIA, 8 Other)	Aortic root/ascending aorta or aortic arch repair	53/121 (44%) developed new vascular lesions.	Cohort not limited to GCA but include other forms of large vessel vasculitis including Takayasu's and clinically isolated aortitis (CIA).

57. In patients with GCA and severe disease, what is the impact of delaying surgical intervention until the disease is in remission on disease-related outcomes and surgical intervention-related adverse events?
    - No single arm data available
    - **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies :

Author	**Year**	**Title**
Mennender	2008	Surgical management of ascending aortic aneurysm due to non-infectious aortitis
Clifford	2019	Outcomes among 196 patients with non-infectious proximal aortitis

- Studies reviewed and excluded:

Author	**Year**	**Title**	**Comments**

M. Gagne-Loranger	2016	Giant cell aortitis: clinical presentation and outcomes in 40 patients consecutively operated on	Exclude: It is not clear from the manuscript if patients had active disease or were in remission at the time of surgery.

Giant Cell Arteritis (GCA)

Surgical Intervention

- **PICO question 26:** In patients with GCA with severe disease, what is the impact of endovascular interventions (such as angioplasty or stent placement) versus vascular bypass or grafting on disease-related outcomes and surgical treatment-related adverse events?

- **Critical Outcomes:** Damage from disease, infection, ischemic events, complications of the intervention such as bleeding or thrombotic events, adverse reaction to contrast exposure, need for additional intervention, death

58. In patients with GCA with severe disease, what is the impact of endovascular interventions (such as angioplasty or stent placement) versus vascular bypass or grafting on disease-related outcomes and surgical treatment-related adverse events?
    - No comparative data available

59. In patients with GCA with severe disease, what is the impact of endovascular interventions (such as angioplasty or stent placement) on disease-related outcomes and surgical treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Long term patency/re-stenosis	Both, 2006	Retrospective observational cohort	Mean follow-up of 24 months (range 5-101)	10 CGA patients with symptomatic large artery involvement undergoing PTA (30 lesions). Germany 1995-2004. 9/10 meeting ACR criteria.	PTA of upper extremity arterial lesion	5/10 with relapsing stenosis (10/30 lesions). Cumulative primary patency rate 65.2% (SE 8.9%). Repeat PTA secondary cumulative success rate 82.6%. Tertiary cumulative success rate 89.7%.	Limited to upper extremity arterial stenosis or occlusion.

						Immediate technical success rate 100%.	
Adverse events	Both, 2006	Retrospective observational cohort	Mean follow-up of 24 months (range 5-101)	10 CGA patients with symptomatic large artery involvement undergoing PTA (30 lesions). Germany 1995-2004. 9/10 meeting ACR criteria.	PTA of upper extremity arterial lesion	Moderate dissection of vessel wall 16/30 vascular lesions. Hematoma at puncture site: 1/10 patients Iatrogenic femoral artery pseudoaneurysm: 1/10	Limited to upper extremity arterial stenosis or occlusion.

60. In patients with GCA with severe disease, what is the impact of vascular bypass or grafting on disease-related outcomes and surgical treatment-related adverse events?

- **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Operative mortality	Mennander, 2008	Observational retrospective cohort	Mean follow-up 4 years	100 patients with histological evidence of GCA or lymphoplasmacytic aortitis on resected ascending aortic aneurysm. 1993-2006. Mayo Clinic cohort	Ascending aorta aneurysm repair.	4/100 deaths
Adverse events	Mennander, 2008	Observational retrospective cohort	Mean follow-up 4 years	100 patients with histological evidence of GCA or lymphoplasmacytic aortitis on resected ascending aortic aneurysm. 1993-2006. Mayo Clinic cohort	Ascending aorta aneurysm repair.	Mediastinitis: 1/100 Reoperation for bleeding: 4/100 Stroke: 4/100 Myocardial infarction: 0/100 Low output syndrome: 4/100 Renal insufficiency: 8/100

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- **Single arm studies and test accuracy studies :**

Author	Year	Title

Mennander	2008	Surgical management of ascending aortic aneurysm due to non-infectious aortitis
Both	2006	Balloon angioplasty of arteries of the upper extremities in patients with extracranial giant-cell arteritis

Giant Cell Arteritis (GCA)

Medical treatment

- **PICO question 27:** In patients with GCA undergoing surgical intervention, what is the impact of high dose prednisone use prior to procedure vs. not using high dose prednisone on disease-related outcomes and surgical intervention-related adverse effects?

- **Critical Outcomes:** Damage from disease, disease activity, infection, ischemic events, complications of the intervention such as bleeding or thrombotic events, need for additional intervention, death

61. In patients with GCA undergoing surgical intervention, what is the impact of high dose prednisone use prior to procedure vs. not using high dose prednisone on disease-related outcomes and surgical intervention-related adverse effects?
    - No comparative data available

62. In patients with GCA undergoing surgical intervention, what is the impact of high dose prednisone use prior to procedure on disease-related outcomes and surgical intervention-related adverse effects?
    - No single arm data available

63. In patients with GCA undergoing surgical intervention, what is the impact of not using high dose prednisone on disease-related outcomes and surgical intervention-related adverse effects?
    - No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

None

Takayasu Arteritis (TAK)

Imaging, laboratory tests, and monitoring

- **PICO question 1:** In patients with TAK, what is the impact of utilizing non-invasive imaging vs. invasive imaging as a disease activity assessment tool on the development of disease-related outcomes and diagnostic testing-related adverse events?

- **Critical Outcomes:** Adverse reactions to contrast exposure such as nephrotoxicity, Complications of the procedure (Bleeding, thrombotic and ischemic events), disease damage, relapse, death, Clinical symptoms

64. In patients with TAK, what is the impact of utilizing non-invasive imaging vs. invasive imaging as a disease activity assessment tool on the development of disease-related outcomes and diagnostic testing-related adverse events?
    No comparative data available

65. In patients with TAK, what is the impact of utilizing non-invasive imaging as a disease activity assessment tool on the development of disease-related outcomes and diagnostic testing-related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Relapse: 109 patients underwent different noninvasive imaging (US, PET, MRI). Patients followed up with US had the highest relapse rate (55%), followed by PET followed by MRI (10%)	Fan, 2016	Single Center	Range 2 – 28 months	51 patients with TAK (46F, 5M); 20 patients had follow up scans	Ultrasound of the carotid arteries	Of the 20 patients with follow up studies, 13 had been active at baseline. Of these 13, 12 got to remission. There were no significant differences in carotid wall thickness or outer carotid diameter. 11 of these 12 patients relapsed. During the relapse, there were no significant differences between carotid wall thickness or outer carotid diameter.
	Grayson, 2018	Single Center	6 months in those that received more than 1 scan	26 TAK patients (44 scans, mean age 31 y, 70% F), 30 GCA patients (67 scans, mean age 69, 70%F)	FDG-PET -2 nuclear med providers interpreted PET scans blinded to clinical data and each other. -2 hour uptake time. -Semiquantitative PETVAS score used (4 segments of aorta, 11 branches, rated as	Patients with PETVAS > 20 had higher rate of future relapse (55% vs 11%)

					compared to the liver uptake)	
	Gudbrandsson, 2017	Population based cohort study (Norway)	The mean time on TNF 42 months.	32 patients with TAK (ACR 1990 or modified Ishikawa criteria), All patients treated with TNF	114 MRI exams (Median 4), 73 US (median 2), 49 PET-CT (median 1)	3/32 (10%) had developed new arterial lesions.
Dissection: in 72 patients who underwent US for follow up, dissection happened in 16.7%	Wang 2016	Retrospective single center study	n/a	72 patients with clinical diagnosis of TAK	Vascular sonography Igrayscale, color Doppler, power Doppler, eFLOW, pulses and continuous wave Doppler) of abd Ao, celiac artery, SMA, IMA, BL renal and iliac arteries, innominate artery, BL subclavian, BL carotid, BL vertebral, BL axillary arteries	12/72 (16.7%) were found to have dissections 7/12 had undergone CTA evaluation before and no dissections were identified by CTA in those patients.
Coronary artery involvement: in 129 patients who underwent Coronary CT angiography, 44-52% had coronary artery involvement	Kang 2014	Retrospective single center study	n/a	111 patients with TAK – ACR 1990 criteria (29% with cardiac symptoms, 71% with no cardiac symptoms)	Coronary CT angiogram	53.2% of patients had coronary arterial lesions at CT (28% coronary ostial stenosis; 37% nonostial arterial coronary stenosis; 8% coronary aneurysm) Cardiac sx, disease activity was not associated with differences in coronary involvement.
	Soto, 2011	Retrospective single center study	n/a	18 patients with TAK (1990 ACR criteria) and angina	Coronary CT angiogram	8/18 (44%) of patients had lesions identified 5/8 went on to have catheter angio (6/6 “significant” CT lesions were confirmed, 1 “nonsignificant” CT lesion was recharacterized as “significant” on catheter angio)
Arterial Progression – appearance of novel lesions or increase in width or length or percent of stenosis: in 41 patients who had MRA scans	Youngstein, 2017	Cross-sectional, observational, prospective (April 2010-Dec 2015), Two centers	24 (IQR: 12-60) months from baseline	26 patients with TAK who had underwent surgery with graft placement	FDG-PET at baseline (23/26 – 88% had significant periprosthetic uptake), MRA scans were performed 24 (IQR: 12-60) months from baseline to assess for vascular progression	1/26 had progression on follow up MRA

for disease assessment, 7% had increased vascular involvement, while in 9 patients with active disease who had PET for follow up, 11% had increased vascular involvement.	Sun, 2016	Single center, cohort	6 months	15 patients with TAK (ACR 1990 criteria) had repeat contrasted MRI studies (11/15 were "active" at baseline)	CE-MRA (dark blood images – vessel wall imaging)	12/15 had no change in arterial involvement 2/15 had increased vascular involvement (both were active at baseline) 1/15 had decreased arterial involvement
	Lee, 2012	Single center cohort (retrospective)	Mean time to follow up scan 4.2 months	13 patients with TAK per 1990 ACR criteria (9/13 with active disease at baseline; 4/13 with inactive disease at baseline)	FDG-PET scan at baseline and follow up	8/9 patients with active disease at baseline had improvement in FDG uptake on follow up after treatment 3/3 patients with inactive disease at baseline (but FDG activity at baseline) had improvement on FDG uptake at follow up 1 patient had increased FDG uptake on flare of disease at follow up.
Disease activity: 68 patients were evaluated using CTA, FDG PET, and US. US detected active disease in 1/6 patients, PET showed reduced uptake in 5/6 patients with remission and had a sensitivity of 40-47% in patents with high CRP and ESR respectively. CTA showed increased wall thickness regardless of ESR and CRP values in 9 patients. 4	Khandelwal 2011	Retrospective analysis of 15 consecutive patients	No follow up	15 patients (8 males, 7 females)	Multidetector CTA Arterial mural thickness correlated to ESR and CRP	Laboratory results available in 9 patients All 9 patients had wall thickness. 6 out of 9 had elevated ESR and CRP and 3 out of 9 had normal ESR and CRP
	Andrews 2003	Retrospective review	1996- 2002	6 newly diagnosed patients (5 females, 1 male)	Conventional IA angiography was compared to MRA or FDG-PET performed at diagnosis and follow up (after therapy)	IA angiography not performed in 1 patient at baseline. All 6 pts had FDG-PET at baseline and follow up. 5 pts had MRA at baseline and at follow up 5 out of 6 pts achieved remission. On all 5 pts in remission FDG-PET was significantly reduced uptake (p,0.04) Only 1 MRA out of 5 pts in remission showed improvement of wall thickness. 1 pt did not achieve remission – FDG-PET continued to show abnormal uptake.
	Webb 2004	Retrospective review	1999-2003	18 pts (17 females, 1 male)	Angiography was compared to FDG-PET	A total of 28 FDG-PET scans were done Compared to combined assessment of disease activity FDG-PET correctly detected 11/12 pts with active disease and all 6 in remission. WSR and CRP elevation also correlated with positive FDG-PET (p=0.05, p=0.0047)
	Maeda 1991	Prospective analysis	No follow up	23 patients (all females)	US of carotids was compared to angiography	46 carotids examined: 34 (74%) had thick IMC pattern. Only 11 carotids and 3 patients without abnormalities. 28 (61%) of 46 carotids and 10 pts (43%) failed to show abnormalities on arteriogram.

studies that included 160 patients with TAK evaluated by differing noninvasive means generally showed that the imaging changed with disease activity, though one study did not show significant change in imaging with respect to active disease.						7 patients had active disease by serology – of those, all but 1 had abnormal US (thick IMC)
	Walter 2005	Prospective Consecutive patients		6 pts (6 females)	Evaluation of FDG-PET in the assessment of disease activity	8 scans done For high CRP - sensitivity of PET was 46.6% For high ESR – sensitivity was 40.3%
	Li, 2019	Consecutive cohort	N/A	71 pts with TAK (60F, 11M, median age 32); ACR criteria	Contrast-enhanced US (CEUS); Semiquantitative method (rated from 0-3)	CEUS grade correlated significantly with NIH ($p<0.001$) and ITAS 2000 ($p=0.004$)
	Banerjee, 2019	Prospective ongoing cohort	6 months in this study	52 pts with LVV (31 GCA, 21 TAK)	FDG-PET exam	In the cohort that had treatment increased over the interval, Median PETVAS significantly improved from baseline to 6-month follow-up visit (23.5 vs 18; $p < 0.01$). Concomitantly, significant improvement in median PGA scores (2 vs 0, $p < 0.01$), CRP (6.2 vs 2.0, $p < 0.001$), and ESR (24 vs 9, $p < 0.0001$) was also observed
	Incerti, 2019	Cross sectional study	NA	30 patients with TAK	FDG-PET exam	Positive PET scan, Number of lesions with significant uptake, and SUVmax were all not significantly different in patients with active disease compared to patients with inactive disease (all $p<0.1$)
	Martinez, 2018	Single Center study	3-12 months repeat PET scan	38 consecutive patients with TAK. One pt excluded due to poor quality images.	FDG-PET exam Target to background ratio (TBR):: TBR:aortic wall uptake divided by blood pool uptake	21/37 patients evaluated (56.8%) Experienced clinical improvement after the initial PET/CT scan and In the 21 patients With clinical improvement the mean TBR decreased significantly from 1.8 ± 0.6 to1.5 ± 0.3 (p ¼ 0.0002).
Aortic Aneurysm/Dilation – One study with 41 patients with TAK showed that noninvasive testing found 20% had aortic dilatation over follow up.	Muratore, 2019	Longitudinal study	30 month, median	93 LVV (41 TAK, 52 GCA) that underwent at least 2 PET exams	90%+ of imaging was noninvasive (PET, CT, MRA)	18 (12 GCA, 6 TAK)/93 (19.4%) were found to have aortic dilatation. No significant predictors found (PET, disease activity, CV risk factors).

- ***Test Accuracy results****:* Use of non-invasive imaging be used to diagnose disease activity in Takayasu patients

Sensitivity	0.72 (95% CI: 0.54 to 0.84)
Specificity	0.69 (95% CI: 0.53 to 0.82)

Prevalence	40%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 40%	pre-test probability of 50%	
True positives (patients with disease activity)	8 studies 180 patients	cohort & case-control type studies	serious [a]	serious [b]	not serious [c]	serious [d]	none	286 (218 to 337)	358 (272 to 421)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having disease activity)								114 (63 to 182)	142 (79 to 228)	
True negatives (patients without disease activity)	8 studies 193 patients	cohort & case-control type studies	serious [a]	serious [b]	not serious [c]	serious [d]	none	416 (320 to 490)	347 (267 to 408)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having disease activity)								184 (110 to 280)	153 (92 to 233)	

- **Explanations**
- a. Due to patient selection (some studies did not avoid inappropriate exclusions), the results of the index test were interpreted with knowledge of the results of the standard reference, and not all patients received a reference test
- b. Indirectly compares the interventions in which we are interested (invasive vs noninvasive) when applied to the populations in which we are interested
- c. The similarity of point estimates and overlap of confidence intervals make inconsistency not serious
- d. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

66. In patients with TAK, what is the impact of utilizing invasive imaging as a disease activity assessment tool on the development of disease-related outcomes and diagnostic testing-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Complications 82 patients with TAK underwent DSA and there were 0 complications	Liu, 1990	Retrospective		50 patients with aorto-arteritis with TAK for mean 16 years underwent digital subtraction angiography	51 patients. IV DSA used in 48 and intra-arterial used in 3	0 complications
	Lacombe, 1986	Retrospective		32 TAK patients. 21 with new dx and 10 post op controls with TAK	IV DSA was performed in all patients to evaluate for vessel abnormalities	0 complications
Visualization/success of imaging 48 (96%) showed good visualization of	Liu, 1990	Retrospective		50 patients with aorto-arteritis with TAK for mean 16 years underwent digital subtraction angiography	51 patients. IV DSA used in 48 and intra-arterial used in 3	Excellent to god visualization obtained in 96%

the 50 patients studied						

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

	Author	Year	Title
Patient important outcomes	Gudbrandsso	2017	TNF inhibitors appear to inhibit disease progression and improve outcome in Takayasu arteritis; an observational, population-based time trend study
	Youngstein	2017	FDG Uptake by Prosthetic Arterial Grafts in Large Vessel Vasculitis Is Not Specific for Active Disease
	Fan	2016	Ultrasound morphological changes in the carotid wall of Takayasu's arteritis: monitor of disease progression
	Wang	2016	Sonographic Characterization of Arterial Dissections in Takayasu Arteritis
	Sun	2016	Value of whole-body contrast-enhanced magnetic resonance angiography with vessel wall imaging in quantitative assessment of disease activity and follow-up examination in Takayasu's arteritis
	Kang	2014	Takayasu arteritis: assessment of coronary arterial abnormalities with 128-section dual-source CT angiography of the coronary arteries and aorta
	Lee	2012	The role of (18) F-fluorodeoxyglucose-positron emission tomography in the assessment of disease activity in patients with Takayasu arteritis
	Soto	2011	Coronary CT angiography in Takayasu arteritis
	Khandelwal	2014	Multidetector CT angiography in Takayasu arteritis
	Andrews	2004	Non-invasive imaging in the diagnosis and management of Takayasu's arteritis
	Maeda	1991	Carotid lesions detected by B-mode ultrasonography in Takayasu's arteritis: "macaroni sign" as an indicator of the disease
	Walter	2005	The value of FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease
	Li	2019	Contrast-enhanced Ultrasonography for Monitoring Arterial Inflammation in Takayasu Arteritis

	Martinez	2018	(18)F-FDG PET/CT in the follow-up of large-vessel vasculitis: A study of 37 consecutive patients
	Banerjee	2019	Effect of Treatment on Imaging, Clinical, and Serologic Assessments of Disease Activity in Large-Vessel Vasculitis
	Incerti	2019	(18)F-FDG PET reveals unique features of large vessel inflammation in patients with Takayasu's arteritis
	Muratore	2019	Aortic dilatation in patients with large vessel vasculitis: A longitudinal case control study using PET/CT
	Liu	1990	Intravenous digital subtraction angiography in patients with aorto-arteritis (Takayasu's)
	Lacombe	1986	Intravenous digital subtraction angiography in Takayasu's disease. A report of 32 cases
Patient important outcomes and test accuracy	Webb	2004	The role of 18F-FDG PET in characterising disease activity in Takayasu arteritis
	Grayson	2018	(18) F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis
Test accuracy studies	Eshet	2011	The limited role of MRI in long-term follow-up of patients with Takayasu's arteritis
	Quinn	2017	Comparison of magnetic resonance angiography and (18)F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis
	John	2017	Correlating MRI with clinical evaluation in the assessment of disease activity of Takayasu's arteritis
	Santhosh	2014	F-18 FDG PET/CT in the evaluation of Takayasu arteritis: an experience from the tropics
	Karapolat	2013	Comparison of F18-FDG PET/CT findings with current clinical disease status in patients with Takayasu's arteritis
	Nguyen	2019	The utility of fluorine-18-fluorodeoxyglucose positron emission tomography in the diagnosis and monitoring of large vessel vasculitis: A South Australian retrospective audit

- Studies reviewed and excluded:

Author	**Year**	**Title**	**Comments**
F. A. Aeschlimann	2017	Childhood Takayasu arteritis: disease course and response to therapy	Exclude for single arm TAK PICO 1, does not address
C. Comarmond	2017	Long-Term Outcomes and Prognostic Factors of Complications in Takayasu Arteritis: A Multicenter Study of 318 Patients	Exclude for single arm TAK PICO 1, no data on type of imaging performed
Y. F. Peng	2017	Serum Bilirubin Concentrations in Patients With Takayasu Arteritis	Exclude for single arm TAK PICO 1, does not address

K. M. Treitl	2017	3D-black-blood 3T-MRI for the diagnosis of thoracic large vessel vasculitis: A feasibility study	Exclude for single arm TAK PICO 1, no relevant outcomes
F. Alibaz-Oner	2016	Plasma pentraxin-3 levels in patients with Takayasu's arteritis during routine follow-up	Exclude for single arm TAK PICO 1, not specific if imaging is invasive or non-invasive
F. Alibaz-Oner	2015	Patients with Takayasu's arteritis having persistent acute-phase response usually have an increased major vessel uptake by 18F-FDG-PET/CT	Exclude for single arm TAK PICO 1
D. Li	2011	Detecting disease extent and activity of Takayasu arteritis using whole-body magnetic resonance angiography and vessel wall imaging as a 1-stop solution	Exclude for single arm TAK PICO 1
M. Both	2008	MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis	Exclude. Not TAK
M. K. Yadav	2007	Takayasu arteritis: clinical and CT-angiography profile of 25 patients and a brief review of literature	Exclude. Does not address the question. Descriptive study of vascular findings. No correlations.
C. Cantu	2000	Noninvasive cerebrovascular assessment of Takayasu arteritis	Exclude. Does not address question. Descriptive study of intracranial involvement.
C. Lefebvre	2000	The role of B-mode ultrasonography and electron beam computed tomography in evaluation of Takayasu's arteritis: a study of 43 patients	Exclude. Does not address question. Descriptive study of usefulness of non-invasive test in detecting stenosis and wall thickening. No correlation with disease activity.
I. Yamada	2000	Takayasu arteritis: diagnosis with breath-hold contrast-enhanced three-dimensional MR angiography	Exclude. Does not address question. Descriptive study of utility of MRA for diagnosis. No correlation with activity.
M. Ando	2000	Surgical considerations of occlusive lesions associated with Takayasu's arteritis	Exclude. Does not address question. Surgical results of occlusive lesions.
R. O. Raninen	2000	Ultrasonography in the quantification of arterial involvement in Takayasu's arteritis	Exclude. Does not address question. Diagnostic performance of UA.
I. Yamada	1998	Takayasu arteritis: evaluation of the thoracic aorta with CT angiography	Exclude. Does not address question. Diagnostic performance of CTA.
J. H. Park	1997	CT angiography of Takayasu arteritis: comparison with conventional angiography	Exclude. Does not address question. Diagnostic performance of CTA.

S. Kumar	1997	Takayasu's arteritis: evaluation with three-dimensional time-of-flight MR angiography	Exclude. Does not address question. Correlation of MRA with arteriogram in terms of detecting vessel abnormalities. No correlation with disease activity.
N. Taniguchi	1997	Comparative ultrasonographic and angiographic study of carotid arterial lesions in Takayasu's arteritis	Exclude. Does not address question. Performance of US in detecting carotid lesions compared to arteriogram. No correlation with disease activity.
Y. Sun	1996	Ultrasonographic study and long-term follow-up of Takayasu's arteritis	Exclude. Does not address question. Descriptive study of use of US over time. No objective measurement of disease activity.
A. Hata	1995	Magnetic resonance imaging of vascular changes in Takayasu arteritis	Exclude. Does not address question. Comparison of MRA abnormalities between TAK and healthy controls.
K. E. Meyers	1994	Gallium scintigraphy in the diagnosis and total lymphoid irradiation of Takayasu's arteritis	Exclude. Does not address question. Evaluation of treatment with total lymphoid irradiation.
K. S. Chugh	1992	Renovascular hypertension due to Takayasu's arteritis among Indian patients	Exclude. Does not address question. Different causes of renovascular HTN.
M. D. B. Spichler	2008	Takayasu's arteritis: Clinical and therapeutic aspects in 36 patients	Exclude. Missing data. One of disease activity measurements was performed in only half of the patients.
E. Albert	2003	Hypertension and Elevated ESR as Diagnostic Features of Takayasu Arteritis in Children	Exclude. Does not address question. Diagnostic performance of WSR and hypertension in predicting the diagnosis of TAK.
T. Wolkanin-Bartnik	2002	Ultrasound examination of carotid arteries with intima media measurement: An underestimated tool in the diagnosis of Takayasu's disease	Exclude. Does not address question. US abnormalities of carotids of pts with TAK compared to controls.

Takayasu Arteritis (TAK)

Imaging, laboratory tests, and monitoring

- **PICO Question 2:** In patients with TAK, what is the impact of adding inflammatory markers to clinical monitoring as a disease activity assessment tool vs. clinical monitoring alone on the development of disease-related outcomes and diagnostic testing-related adverse

events?

- **Critical Outcomes:** Active disease, Clinical symptoms, Relapse, Death, organ damage

67. In patients with TAK, what is the impact of adding inflammatory markers to clinical monitoring as a disease activity assessment tool vs. clinical monitoring alone on the development of disease-related outcomes and diagnostic testing-related adverse events?
    - No comparative data available.

68. In patients with TAK, what is the impact of adding inflammatory markers to clinical monitoring as a disease activity assessment tool on the development of disease-related outcomes and diagnostic testing-related adverse events
    - Patient important outcomes:

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Results
Active disease	Comarmond C, 2017	Retrospective observational	Median 6.1 years	318 French TAK patients meeting ACR and Ishikawa criteria modified by Sharma	Progressive clinical course in 124 of 318 patients (39.0%); Vascular complications in 122 of 318 patients (38.3%)
Relapse					136 patients relapsed (136/318, 42.8%)
Death					16 deaths out of 318 patients (5%)
Organ damage	Keskek S, 2017	Cross sectional	NA	12 Turkish TAK patients meeting ACR criteria	Acrotism (pulselessness disease) in 4/12 and 8/12 without acrotism. ESR (mm/h) with acrotism 36.0±14.4 vs w/o 13.1±7.7. CRP (mg/L) with acrotism 7.9±5.1 vs 3.8±1.6.
	Wang X, 2016	Case controlled	Median f/u 3.2 yrs ±2.1	60 Chinese TAK patients meeting ACR criteria seen between 2005-2014	MACE (major adverse cardiac events) associated with Log(hsCRP) with HR 5.3 (95% CI 1.1-27.8;p=0.04)

- Test Accuracy results for inflammatory markers in active and inactive disease:

Sensitivity	0.75 (95% CI: 0.63 to 0.84)
Specificity	0.75 (95% CI: 0.64 to 0.84)

Prevalence	45.85%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 45.85%	
True positives (patients with [target condition])	4 studies 84 patients	cohort & case-control type studies	not serious	not serious	serious	serious	none	343 (290 to 383)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having [target condition])								116 (76 to 169)	
True negatives (patients without [target condition])	4 studies 86 patients	cohort & case-control type studies	not serious	not serious	serious	serious	none	408 (344 to 456)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having [target condition])								134 (86 to 198)	

69. In patients with TAK, what is the impact clinical monitoring alone on the development of disease-related outcomes and diagnostic testing-related adverse events?
    - No single available data

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Included Studies:

Single Arm	Author	Year	Title
	Comarmond, C	2017	Long-Term Outcomes and Prognostic Factors of Complications in Takayasu Arteritis: A Multicenter Study of 318 Patients
	Keskek	2017	High Levels of Circulating Endothelial Progenitor Cells Are Associated with Acrotism in Patients with Takayasu Arteritis
	Wang	2016	High-sensitivity C-reactive protein predicts adverse cardiovascular events in patients with Takayasu arteritis with coronary artery involvement
Test Accuracy Studies	Dagna, L	2011	Pentraxin-3 as a marker of disease activity in Takayasu arteritis
	Matasuyama, A	2003	Matrix metalloproteinases as novel disease markers in Takayasu arteritis
	Ishihara, T	2013	Diagnosis and assessment of Takayasu arteritis by multiple biomarkers
	Ma, J	2003	Circulation levels of acute phase proteins in patients with Takayasu arteritis
	Chen	2019	Assessment of disease activity in Takayasu arteritis: A quantitative study with computed tomography angiography

- Studies reviewed and excluded:

Author	Year	Title	Comments
R. Goel	2018	Study of serial serum myeloid-related protein 8/14 as a sensitive biomarker in Takayasu arteritis: a single centre study	Exclude: Outcomes of interest not reported.
F. A. Aeschlimann	2017	Childhood Takayasu arteritis: disease course and response to therapy	Exclude: It is not clear from the manuscript how many of the patients were getting regular inflammatory markers.
L. Pan	2017	Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio associated with disease activity in patients with Takayasu's arteritis: a case-control study	Exclude: Outcomes of interest not included. Only looks at outcomes in relation to Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratio.
F. Alibaz-Oner	2016	Plasma pentraxin-3 levels in patients with Takayasu's arteritis during routine follow-up	Exclude: Outcomes of interest not reported regarding ESR and CRP. Levels of Pentraxin-3 were reported during active and inactive disease.

X. Kong	2016	The critical role of IL-6 in the pathogenesis of Takayasu arteritis	Exclude: Outcomes of interest not included.
X. Kong	2015	Evaluation of clinical measurements and development of new diagnostic criteria for Takayasu arteritis in a Chinese population	Exclude: Accuracy study for diagnostic criteria of TAK in Chinese population.
S. Dogan	2014	Markers of endothelial damage and repair in Takayasu arteritis: are they associated with disease activity?	Exclude: Outcomes of interest not included.
H. Yilmaz	2012	Ghrelin and adipokines as circulating markers of disease activity in patients with Takayasu arteritis	Excluded: Outcomes of interest not included.
T. Ishihara	2013	Diagnosis and assessment of Takayasu arteritis by multiple biomarkers	Excluded: accuracy study for biomarkers including hsCRP, MMP6 and Pentraxin 3
P. C. Grayson	2012	Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis	Exclude: Does not address the PICO. Also, much of the data is in regard to accuracy of testing.
B. F. Hoyer	2012	Takayasu arteritis is characterised by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab	Exclude: outcomes of interest not reported.
W. F. Ng	2006	Takayasu's arteritis: a cause of prolonged arterial stiffness	Exclude: Outcomes of interest were not included.
K. E. Meyers	1994	Gallium scintigraphy in the diagnosis and total lymphoid irradiation of Takayasu's arteritis	Exclude: Outcomes of interest were not included.
K. S. Chugh	1992	Renovascular hypertension due to Takayasu's arteritis among Indian patients	Exclude: Outcomes of interest were not included
M. D. B. Spichler	2008	Takayasu's arteritis: Clinical and therapeutic aspects in 36 patients	Exclude: Study does not answer the PICO question.
E. Albert	2003	Hypertension and Elevated ESR as Diagnostic Features of Takayasu Arteritis in Children	Exclude: Study only includes 6 Takayasu patients and compares them to historic controls in the literature. Very limited data regarding inflammatory markers.
Ma Walter	2005	The value of FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease	Exclude: Inflammatory markers were correlated to uptake by PET but there is no correlations done on outcomes of interest.

Takayasu Arteritis (TAK)

Imaging, laboratory tests, and monitoring

- **PICO question 3:** In patients with known TAK, what is the impact of regularly scheduled non-invasive imaging (e.g., every 6 months) vs. routine clinical assessment on the development of disease-related outcomes and diagnostic testing-related adverse events?

- **Critical Outcomes**: Adverse reactions to contrast exposure, adverse reactions to sedation, Active disease, relapse, death, disease damage, clinical symptoms, patient reported outcomes.

70. In patients with known TAK, what is the impact of regularly scheduled non-invasive imaging (e.g., every 6 months) vs. routine clinical assessment on the development of disease-related outcomes and diagnostic testing-related adverse events??
    - No comparative data available.

71. In patients with known TAK, what is the impact of regularly scheduled non-invasive imaging (e.g., every 6 months) on the development of disease-related outcomes and diagnostic testing-related adverse events?
    - Patient important outcomes:

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Active disease PET is able to identify active disease; Increase in FDG uptake observed in TAK patients with increased acute phase reactants. that included 160 patients with TAK evaluated by differing noninvasive means generally showed that the imaging changed with disease activity,	Walter, 2005	Retrospective	Not specified	26 patients with TAK (n=6) or GCA evaluated with PET.	26 patients and 26 controls underwent PET. 4 patients had follow up scans. 26 age and gender matched controls evaluated with PET. PET uptake graded on 4 point scale and correlated with ESR and CRP	No grade 2 or 3 uptake in controls. Grade 1 uptake correlated with ESR of 6, Grade 2 uptake in patients correlated with ESR of 46, and grade 3 with ESR of 90 (p=0.007). Grade 1 arteritis correlated with CRP of 4.0, Grade 2 with CRP of 37 and grade 3 with CRP of 172 (p=0.002). Follow up PET in 4 patients with tx had decrease in ESR/CRP and reduction in PET activity	PET able to identify active disease and correlated with both ESR and CRP, but more with CRP. PET improved in follow up of 4 treated patients. Only 6 TAK patients total
	Alibaz Oner, 2015	retrospective		14 patients with clinically inactive TAK, but persistent	All patients underwent FDG PET.	Active vasculitic lesions observed in 9/14 (64.3% of patients. Median number	Increase in FDG uptake in the majority of TAK patients with an increase in

though one study did not show significant change in imaging with respect to active disease.				elevation of acute phase reactants		of active vascular lesions was 2.	acute phase reactants but clinically silent disease.
	Youngstein T, 2017	Observational prospective	2 years	26 TAK patients >6 months after graft surgery	Underwent PET/FDG imaging of graft and native arteries and compared active and inactive disease as well as arterial progression assessed by MRA	High frequency of graft associated FDG uptake, but no progression in MRAs Median uptake higher in grafts than native aorta p<0.001) FDG uptake did not reflect activity status	FDG uptake in areas of arterial grafts do not have clinical significance (in terms of disease activity or progression)
	Li, 2019	Consecutive cohort	N/A	71 pts with TAK (60F, 11M, median age 32); ACR criteria	Contrast-enhanced US (CEUS); Semiquantitative method (rated from 0-3)	CEUS grade correlated significantly with NIH (p<0.001) and ITAS 2000 (p=0.004)	Indirect Disease Activity by ITAS-A or NIH
	Banerjee, 2019	Prospective ongoing cohort	6 months in this study	52 pts with LVV (31 GCA, 21 TAK)	FDG-PET exam	In the cohort that had treatment increased over the interval, Median PETVAS significantly improved from baseline to 6-month follow up visit (23.5 vs 18; p < 0.01). Concomitantly, significant improvement in median PGA scores (2 vs 0, p < 0.01), CRP (6.2 vs 2.0, p < 0.001), and ESR (24 vs 9, p < 0.0001) was also observed	Indirect PETVAS (graded evaluation per vascular territories)
	Incerti, 2019	Cross sectional study	NA	30 patients with TAK	FDG-PET exam	Positive PET scan, Number of lesions with significant uptake, and SUVmax were all not significantly different in patients with active disease compared to patients with inactive disease (all p<0.1)	Indirect NIH criteria was disease activity measure. FYI, PET was used in clinical practice to guide treatment.
	Martinez, 2018	Single Center study	3-12 months repeat PET scan	38 consecutive patients with TAK. One pt excluded due to poor quality images.	FDG-PET exam Target to background ratio (TBR):: TBR:aortic wall uptake divided by blood pool uptake	21/37 patients evaluated (56.8%) experienced clinical improvement after the initial PET/CT scan and in the 21 patients with clinical improvement the mean TBR decreased significantly	Indirect No specified definitions for “clinical improvement”

						from 1.8 ± 0.6 to1.5 ± 0.3 (p ¼ 0.0002).	
Disease progression Repeat ultrasound may be helpful; MRI and MRI limited in the role of long-term follow up; Whole body cE-MRI can quantitively assess disease activity; US of carotids not statistically corelated to disease activity.	Sun, 1995	retrospective	Average duplex follow up period ws 52.7 months. Mean follow up from dz's onset 17.1 years	16 female patients with TAK. 6 with repeat doppler studies (2-10 examinations)	Clinical features analyzed. All patients had undergone at least one duplex scan evaluating brachiocep, extracranial, vertebral and subclav a. 6 underwent sequential duplex exam and long term clin follow up	All patients had subclav a. involvement. Circumferential intima-media thickening seen in stenotic common carotid a (11/16,89%). In serial follow up 2 of 6 had progressive vascular stenosis with concentric thickening in B common carotid a. other 4 were clinically stable and duplex showed non-progression. Of 16 patients, 4 had CCA occlusion (2 of these had progressive blurred vision).	Repeat ultrasound imaging was helpful in detecting progression of lesions
	Kumar, 1997	Retrospective test accuracy study	9-12 months	16 TAK patients, follow up performed in 3	MRA performed in 16 TAK patients and compared with angiography. Follow up MRA done in 3 patients after 9-12 months	Correlation found between MRA findings and contrast angiography in 129 of 145 arteries. Follow up in 3 patients at 9-12 months showed new lesion in LCA in one patient, no change in 2nd patient and insignificant stenosis in L subclav in 3rd patients. No AEs	Mostly test accuracy but follow up in 3 patients showed changes in 2 on MRA. No adverse outcomes
	Eshet Y, 2011	Retrospective	Avg 36 months (12-56 month)	11 TAK patients with clinical data and repeat MRI studies	Clinical data of 11 TAK patients matched with MRI studies. MRI + if e/o arterial wall enhancement, anatomic changes (dilation, stenosis, occlusion or wall irregularity). Disease activity determined by localizing ischemic signs/symptoms, systemic signs and inc ESR, CRP)	47 MRI exams in 11 patients. MRI positive for active disease at least once in 9/11 patients (82%). No correlation between clinical activity and MRI signs of activity	MRI useful in primary dx of TA, but limited role in long term follow up when reactivation is suspected
	Lee K, 2012	Retrospective chart review	Data collected over 8	38 patients with TAK with baseline PET	Clinical disease activity measured at baseline and c/w PET scan. Those with	Active PET (grade>2) observed in 18/24 patients with active disease and 5 of	FDG uptake is associated with clinical disease activity/markers of

			years. Time from first PET to repeat was 4.19 months +/-2.5 months	scan, 15 had follow up PET	follow up PET (n=15) had results compared with clinical activity at the time	14 patients with inactive disease. Association between clinical disease activity and PET (p=0.008). In 15 follow up PET scans, after tx, decrease in visual grade (p=0.011), areas of active vascular uptake (p=0.028) and standard uptake value intensity (p=0.008) reflected changes in clinical disease activity	inflammation and reflects changes in clinical activity in patients with TA
	Sun Y, 2016	Retrospective		52 TA patients (5m, 47f, avg age 33). repeat imaging in 15 patients after 6 months	All patients underwent whole body CE-MRI (n=52) with follow up imaging in 15 patients after 6 months. Images were quantitatively scored and compared with clinical disease activity (ITAS 2010, ESR, CRP, pentraxin-3 levels)	In 15 follow up patients at 6 months: at baseline 11 patients were active and 7 went into remission. Clinical manifestations improved with treatment (p<0/05), ESR and CRP decreased significantly (p=0.04, p=0.02). Whole body CE MRI showed no differences between quantitative MR score for luminal stenosis (p=0.12), wall thickening (p=0.27) before or after the follow up. However, wall enhancement scores decreased significantly (p=0.04)	Whole body cE-MRI with vessel wall imaging detects luminal changes and vessel wall inflammation in TA and can quantitatively assess TA activity (with follow up)
	Fan, 2016	Retrospective, but prospective follow up in 20 patients	2 months-28 months	51 TAK patients assessed with carotid US. 20 patients underwent follow up exams	Underwent 2-5 examinations with ultrasound	Baseline 13/20 were active. Carotid wall thickness (p=0.15) and outer diameter (p=0.05) were decreased with clinical treatment. No AesRelapse in 11/12 patients showed thicker carotid walls (p=0.13) and inc outer carotid diameter (p=0.09)	US of carotids correlated with clinical disease activity and remission but did not reach stat significance. No AEs
Survival	Soto, 2006	retrospective	Not specified	76 mexican mestizo patients with TA	TTE done in all patients. Angiography done ~5 days after ECHO	5 year survival of patients with LV concentric hypertrophy was 80%	24% lost to follow up. ECHO able to detect abnormalities that

						compared to 95% in those without hypertrophy (p=0.00). 13 of 76 (17%) of patients died. 85% were hypertensive and 9%(n=15) also had acute MI. 11/15 were less than 40yo with no coronary risk factors. 7 of 15 AMI had aortic regurg	predispose to death and AMI in TAK
Aortic Aneurysm/Dilation – One study with 41 patients with TAK showed that noninvasive testing found 20% had aortic dilatation over follow up.	Murator e, 2019	Longitudinal study	30 month, median	93 LVV (41 TAK, 52 GCA) that underwent at least 2 PET exams	90%+ of imaging was noninvasive (PET, CT, MRA)	18 (12 GCA, 6 TAK)/93 (19.4%) were found to have aortic dilatation. No significant predictors found (PET, disease activity, CV risk factors).	

- Test Accuracy:

Author, year	Patient Selection	Risk of bias	Index Test	Risk of bias	Reference Standard	Risk of bias	Flow and timing Rsk of bias	Sens	Spec	PPV	NPV
Tezuka D 2012	39 TA patients undergoing PET/CT between 2006-2010.	Low	FDG/PET CT evaluating max SUV in active (n=27) vs inactive cases (n=12) and control subjects (n-40)	Low	Biomarkers including CRP and ESR along with disease activity defined by NIH criteria (systemic features, inc esr, vascular ischemia, angiographic changes)	unclear	Low (scored within 1 month of each other)	92.6%	91.7%	96.2%	84.6%
Papa 2012	23 consecutive patients with TAK underwent MRA between 2006-2009	Low	MRA (cutoff of 40%)	Unclear (no prespecified cutoff)	Reference standard based on Kerr criteria (clinical lab, angiographic evidence, not widely validated)	High	Low	100%	89%	92%	100%

Question: Should PET/CT be used to diagnose ACTIVE DISEASE in TAK?

Sensitivity	0.91 (95% CI: 0.83 to 0.96)
Specificity	0.92 (95% CI: 0.79 to 0.98)

Prevalence	20%	30%	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 30%	
True positives (patients with ACTIVE DISEASE)	1 studies 83 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	182 (166 to 192)	273 (249 to 288)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having ACTIVE DISEASE)								18 (8 to 34)	27 (12 to 51)	
True negatives (patients without ACTIVE DISEASE)	1 studies 40 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	736 (632 to 784)	644 (553 to 686)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having ACTIVE DISEASE)								64 (16 to 168)	56 (14 to 147)	

1- Tezuka, D 2012

72. In patients with known TAK, what is the impact of routine clinical assessment on the development of disease-related outcomes and diagnostic testing-related adverse events?
    - No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:

Single Arm	Author	Year	Title
	Jiang, W	2017	FDG Uptake by Prosthetic Arterial Grafts in Large Vessel Vasculitis Is Not Specific for Active Disease

	Fan, W	2016	Ultrasound morphological changes in the carotid wall of Takayasu's arteritis: monitor of disease progression
	Alibaz-Oner, F	2015	Patients with Takayasu's arteritis having persistent acute-phase response usually have an increased major vessel uptake by 18F-FDG-PET/CT
	Sun, Y	2016	Value of whole-body contrast-enhanced magnetic resonance angiography with vessel wall imaging in quantitative assessment of disease activity and follow-up examination in Takayasu's arteritis
	Lee, K	2012	The role of (18) F-fluorodeoxyglucose-positron emission tomography in the assessment of disease activity in patients with takayasu arteritis
	Eshet, Y	2012	The limited role of MRI in long-term follow-up of patients with Takayasu's arteritis
	Soto, M	2006	Echocardiographic follow-up of patients with Takayasu's arteritis: five-year survival
	Sun, Y	1996	Ultrasonographic study and long-term follow-up of Takayasu's arteritis
	Walter, M	2005	The value of FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease
	Li	2019	Contrast-enhanced Ultrasonography for Monitoring Arterial Inflammation in Takayasu Arteritis
	Banerjee	2019	Effect of Treatment on Imaging, Clinical, and Serologic Assessments of Disease Activity in Large-Vessel Vasculitis
	Incerti	2019	(18)F-FDG PET reveals unique features of large vessel inflammation in patients with Takayasu's arteritis
	Martinez	2018	(18)F-FDG PET/CT in the follow-up of large-vessel vasculitis: A study of 37 consecutive patients
	Muratore	2019	Aortic dilatation in patients with large vessel vasculitis: A longitudinal case control study using PET/CT
Test Accuracy Studies	Tezuka D	2012	Role of FDG PET-CT in Takayasu Arteritis Sensitive Detection of Recurrences
	Papa	2012	Takayasu Arteritis: Intravascular Contrast Medium for MR Angiography in the Evaluation of Disease Activity

- Studies reviewed and excluded:

Author	**Year**	**Title**	**Comments**
A. Gulcu	2017	Long-Term Follow-Up of Endovascular Repair in the Management of Arterial Stenosis Caused by Takayasu's Arteritis	Exclude. Does not report specifics on imaging data. Imaging used as follow up

			post endovascular repair to assess for stenosis
K. M. Treitl	2017	3D-black-blood 3T-MRI for the diagnosis of thoracic large vessel vasculitis: A feasibility study	Exclude: Only 11 had TAK and results not stratified by those with TAK. MRI of vasculitis vs controls. Also, c/w CDUS and clin dx
J. Wang	2016	Sonographic Characterization of Arterial Dissections in Takayasu Arteritis	Exclude: does not answer PCIO 3. Eval of dissection with US. 72 patients with clin dx of TAK, evaluated with sonography. 56 had TTE. 12 had arterial dissections. Evaluated with sonography and TTE
X. Kong	2015	Evaluation of clinical measurements and development of new diagnostic criteria for Takayasu arteritis in a Chinese population	Exclude: does not answer PICO 3
F. Alibaz-Oner	2015	Patients with Takayasu's arteritis having persistent acute-phase response usually have an increased major vessel uptake by 18F-FDG-PET/CT	Increase in FDG uptake in the majority of TAK patients with an increase in acute phase reactants but clinically silent disease.
E. J. Kang	2014	Takayasu arteritis: assessment of coronary arterial abnormalities with 128-section dual-source CT angiography of the coronary arteries and aorta	Exclude: done at one time point only
P. C. Grayson	2012	Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis	Exclude: correlation between physical exam and findings on angiogram done at one time point
B. F. Hoyer	2012	Takayasu arteritis is characterised by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab	Exclude: not relevant to PICO 3
Y. Eshet	2011	The limited role of MRI in long-term follow-up of patients with Takayasu's arteritis	MRI useful in primary dx of TA, but limited role in long term follow up when reactivation is suspected
D. Li	2011	Detecting disease extent and activity of Takayasu arteritis using whole-body magnetic resonance angiography and vessel wall imaging as a 1-stop solution	Exclude: minimal longitudinal data (3 patients only) and no time frame reported

A. Hata	1995	Magnetic resonance imaging of vascular changes in Takayasu arteritis	Exclude: no scheduled repeat imaging
M. D. B. Spichler	2008	Takayasu's arteritis: Clinical and therapeutic aspects in 36 patients	Exclude: Descriptive. No longitudinal data on imaging or clinical exam

Takayasu Arteritis (TAK)

Imaging, laboratory tests, and monitoring

- **PICO question 4:** In patients with TAK in apparent remission, what is the impact of long-term routine clinical monitoring (e.g., every 3 months) versus no routine clinical monitoring on disease-related outcomes?

- **Critical Outcomes**: Relapse, Patient reported outcomes, organ damage from disease, death, disease activity

73. In patients with TAK in apparent remission, what is the impact of long-term routine clinical monitoring (e.g., every 3 months) versus no routine clinical monitoring on disease-related outcomes?
    No comparative data available

74. In patients with TAK in apparent remission, what is the impact of long-term routine clinical monitoring (e.g., every 3 months) on disease-related outcomes? No single arm data or test accuracy data available

75. In patients with TAK in apparent remission, what is the impact of no routine clinical monitoring on disease-related outcomes?
    No single arm data or test accuracy data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

Takayasu Arteritis (TAK)

Treatment

- **PICO question 5:** In patients with TAK with active disease, what is the impact of treatment with high-dose glucocorticoids vs. low-dose glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, toxicity leading to drug discontinuation

76. In patients with TAK with active disease, what is the impact of treatment with high-dose glucocorticoids vs. low-dose glucocorticoids on disease-related outcomes and treatment-related adverse events?

77. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	low-dose glucocorticoids (<30mg/d)	high-dose glucocorticoids (>30mg/d)	Relative (95% CI)	Absolute (95% CI)		
Relapse												
1	observational studies	not serious	not serious	not serious	serious [a]	strong association	20/39 (51.3%)	18/57 (31.6%)	OR 2.28 (0.98 to 5.28)	**197 more per 1,000** (from 4 fewer to 393 more)	⨁⨁◯◯ LOW	
Death												
1	observational studies	not serious	not serious	not serious	very serious [a]	none	2/39 (5.1%)	3/57 (5.3%)	OR 0.97 (0.15 to 6.11)	**1 fewer per 1,000** (from 44 fewer to 201 more)	⨁◯◯◯ VERY LOW	
Serious Adverse Events												
1	observational studies	not serious	not serious	not serious	serious [a]	strong association	22/39 (56.4%)	45/57 (78.9%)	OR 0.35 (0.14 to 0.85)	**222 fewer per 1,000** (from 445 fewer to 28 fewer)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Clinical action may differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

Author	Year	Title
Mutoh	2019	Insufficient use of corticosteroids without immunosuppressants results in higher relapse in Takayasu arteritis

Takayasu Arteritis (TAK)

Treatment

- **PICO question 6:** In patients with active TAK not on immunosuppression, what is the impact of initiating treatment with pulse intravenous glucocorticoids followed by high dose oral glucocorticoids vs. high dose oral glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, toxicity leading to drug discontinuation

78. In patients with active TAK not on immunosuppression, what is the impact of initiating treatment with pulse intravenous glucocorticoids followed by high dose oral glucocorticoids vs. high dose oral glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
    No comparative data available

79. In patients with active TAK not on immunosuppression, what is the impact of initiating treatment with pulse intravenous glucocorticoids followed by high dose oral glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No single arm data available

80. In patients with active TAK not on immunosuppression, what is the impact of initiating treatment with high dose oral glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

  None

Takayasu Arteritis (TAK)

Treatment

- **PICO question 7:** In patients with active TAK, what is the impact of glucocorticoid + non-glucocorticoid non biologic immunosuppressive therapy vs. glucocorticoid monotherapy on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes**: Disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation

81. In patients with active TAK, what is the impact of glucocorticoid + non-glucocorticoid non biologic immunosuppressive therapy vs. glucocorticoid monotherapy on disease-related outcomes and treatment-related adverse events?
    No comparative data available

82. In patients with active TAK, what is the impact of glucocorticoid + non-glucocorticoid non biologic immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?
    - **Patient Important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Flares	Aeshlimann, 2017	Comparative observational	At least 24 months	A total of 27 children with TAK (74%	4/27 children (15%) received high-dose corticosteroids only, and 18 (67%) received a combination of corticosteroids plus another	19 flares occurred during 44 non-biologic treatment episodes (43%) compared to only	Results reported for Biologics Vs non biologics, that is why it's not a comparative study, since GCs alone

				females) were included. 22 children (81%) had evidence of active disease at diagnosis. The median age at diagnosis was 12.4 years (IQR 9.1–14.4).	immunosuppressive agent. These immunosuppressive agents prescribed in combination with cortico-steroids included MTX in ten (37%), cyclophosphamide in five (19%), and MTX plus a biologic agent in three (11%) children.	two flares during 12 biologic treatment episodes (17%). (p = 0.18; OR 3.80, 95% CI 0.81–18.59	results are not presented
2-year flare-free survival	Aeshlimann, 2017	Comparative observational	At least 24 months	A total of 27 children with TAK (74% females) were included. 22 children (81%) had evidence of active disease at diagnosis. The median age at diagnosis was 12.4 years (IQR 9.1–14.4).	4/27 children (15%) received high-dose corticosteroids only, and 18 (67%) received a combination of corticosteroids plus another immunosuppressive agent. These immunosuppressive agents prescribed in combination with cortico-steroids included MTX in ten (37%), cyclophosphamide in five (19%), and MTX plus a biologic agent in three (11%) children.	80% with biologic treatments compared to 43% in non-biologic treatments when adjusted for the number of treatment episodes per patient (p = 0.03)	Results reported for Biologics Vs non biologics, that is why it's not a comparative study, since GCs alone results are not presented

83. In patients with active TAK, what is the impact of glucocorticoid monotherapy on disease-related outcomes and treatment-related adverse events?

- **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Number of patients with	Nakaoka, 2017	Randomized	56 weeks	32 Patients 12 years of age or older (obtained from 24 September	Patients were randomly assigned (1:1) using a permuted block method to receive weekly injections of tocilizumab 162mg or placebo subcutaneously; background oral GC dose was	2/18 patients on GCs had SAEs: Eye disorders,

Serious Adverse Events		controlled trial		2014) with diagnoses of TAK.	tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day according to the following formula: GC dose at week n=$0.9^{(N-3)}$ (GC dose at baseline) when n≥4.	Gastrointestinal disorders, vascular disorders
Infections/infestations	Nakaoka, 2017	Randomized controlled trial	56 weeks	32 Patients 12 years of age or older (obtained from 24 September 2014) with diagnoses of TAK.	Patients were randomly assigned (1:1) using a permuted block method to receive weekly injections of tocilizumab 162mg or placebo subcutaneously; background oral GC dose was tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day according to the following formula: GC dose at week n=$0.9^{(N-3)}$ (GC dose at baseline) when n≥4.	9/18 patients on GCs had infections/infestations
Number of Relapses (33 patients received GCs, out of which 61-67% had relapses)	Nakaoka, 2017	Randomized controlled trial	56 weeks	32 Patients 12 years of age or older (obtained from 24 September 2014) with diagnoses of TAK.	Patients were randomly assigned (1:1) using a permuted block method to receive weekly injections of tocilizumab 162mg or placebo subcutaneously; background oral GC dose was tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day according to the following formula: GC dose at week n=$0.9^{(N-3)}$ (GC dose at baseline) when n≥4.	11/18 patients on GCs had relapses
	Langford, 2017	Randomized Controlled trial	40 months	34 eligible patients with TAK were enrolled	Treated with prednisone and abatacept; 26 reached the week 12 randomization and underwent a blinded randomization to abatacept or placebo.	10/15 patients on GCs had relapses
Number of serious Adverse Events (33 patients received GCs, with a total of 12 adverse events, with high	Nakaoka, 2017	Randomized controlled trial	56 weeks	32 Patients 12 years of age or older (obtained from 24 September 2014) with diagnoses of TAK.	Patients were randomly assigned (1:1) using a permuted block method to receive weekly injections of tocilizumab 162mg or placebo subcutaneously; background oral GC dose was tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day according to the following formula: GC dose at week n=$0.9^{(N-3)}$ (GC dose at baseline) when n≥4.	3/18 SAEs were observed in patients on GCs: Eye disorders, Gastrointestinal disorders, vascular disorders

inconsistency in the results)	Langford, 2017	Randomized Controlled trial	40 months	34 eligible patients with TAK were enrolled	Treated with prednisone and abatacept; 26 reached the week 12 randomization and underwent a blinded randomization to abatacept or placebo.	9/15 SAEs were observed in patients on GCs (Ischemic colitis, rectal bleeding, pyelonephritis, Chest pain, epiglottitis, appendicitis, N/V/Diarrhea due to infection, Dyspnea/dysphagia due to reflux)
Median duration of remission	Langford, 2017	Randomized Controlled trial	40 months	34 eligible patients with TAK were enrolled	Treated with prednisone and abatacept; 26 reached the week 12 randomization and underwent a blinded randomization to abatacept or placebo.	5.7 months (+/- 2.69)

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

Author	Year	Title
Nakaoka	2017	Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study)
Langford	2017	A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Takayasu Arteritis
Aeshlimann	2017	Childhood Takayasu arteritis: disease course and response to therapy

Takayasu Arteritis (TAK)

Treatment

- **PICO question 8:** In patients with active TAK, what is the impact of tocilizumab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Clinical symptoms, disease activity, relapse, death, damage from disease, serious adverse events from medication (e.g., Intestinal perforations), infection, malignancy, toxicity leading to drug discontinuation

84. In patients with active TAK, what is the impact of tocilizumab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No comparative data available

85. In patients with active TAK, what is the impact of tocilizumab + glucocorticoid on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Number of patients with Serious Adverse Events – In 2 studies 1/18 and 2/46 patients on Tocilizumab had serious adverse events (eyes disorders, severe neutropenia)	Nakaoka, 2017	Randomized controlled trial	56 weeks	32 Patients 12 years of age or older (obtained from 24 September 2014) with diagnoses of TAK.	Patients were randomly assigned (1:1) using a permuted block method to receive weekly injections of tocilizumab 162mg or placebo subcutaneously; background oral GC dose was tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day according to the following formula: GC dose at week n=$0.9^{(N-3)}$ (GC dose at baseline) when n≥4.	1/18 patients on Tocilizumab + GCs had SAEs (eye disorders)
	Mekinian, 2018	Retrospective multicenter study	36 months	46 patients with TAK (median age 43; 35F)	Tocilizumab. Tocilizumab was mainly used intravenously at 8 mg/kg monthly.	Two (4%) cases required treatment discontinuation, including neoplasm and one severe asymptomatic neutropenia.
Infections/infestations	Nakaoka, 2017	Randomized controlled trial	56 weeks	32 Patients 12 years of age or older (obtained from 24 September 2014) with diagnoses of TAK.	Patients were randomly assigned (1:1) using a permuted block method to receive weekly injections of tocilizumab 162mg or placebo subcutaneously; background oral GC dose was tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day according to the following formula: GC dose at week n=$0.9^{(N-3)}$ (GC dose at baseline) when n≥4.	6/18 patients on Tocilizumab + GCs had infections/infestations
Number of Relapses One study of 46 patients showed relapse rate of 6%,	Nakaoka, 2017	Randomized controlled trial	56 weeks	32 Patients 12 years of age or older (obtained from 24 September 2014)	Patients were randomly assigned (1:1) using a permuted block method to receive weekly injections of tocilizumab 162mg or placebo	8/18 patients on Tocilizumab + GCs had relapses

which was lower than just DMARDs in the study, whereas another study with 32 patients showed a relapse rate of 44% in the Tocilizumab group.				with diagnoses of TAK.	subcutaneously; background oral GC dose was tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day according to the following formula: GC dose at week $n=0.9^{(N-3)}$ (GC dose at baseline) when n≥4.	
	Mekinian, 2018	Retrospective multicenter study	3 years	46 patients with TAK (median age 43; 35F)	Tocilizumab. Tocilizumab was mainly used intravenously at 8 mg/kg monthly.	The cumulative incidence of relapse was significantly higher under DMARDs therapy compared to tocilizumab (34.6% vs 6.3%; p = 0.049, respectively)
Number of serious Adverse Events	Nakaoka, 2017	Randomized controlled trial	56 weeks	32 Patients 12 years of age or older (obtained from 24 September 2014) with diagnoses of TAK.	Patients were randomly assigned (1:1) using a permuted block method to receive weekly injections of tocilizumab 162mg or placebo subcutaneously; background oral GC dose was tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day according to the following formula: GC dose at week $n=0.9^{(N-3)}$ (GC dose at baseline) when n≥4.	1/18 SAEs were observed in patients on Tocilizumab + GCs (eye disorders)
Treatment Response- One study with 46 patients showed two thirds of patient will have a treatment response.	Mekinian, 2018	Retrospective multicenter study	36 months	46 patients with TAK (median age 43; 35F)	Tocilizumab. Tocilizumab was mainly used intravenously at 8 mg/kg monthly.	12/36 (67%) had a treatment response.
Survival – In one study of 46 patients, rate of three-quarters of patients were still on drug at two years without event.	Mekinian, 2018	Retrospective multicenter study	3 years	46 patients with TAK (median age 43; 35F)	Tocilizumab. Tocilizumab was mainly used intravenously at 8 mg/kg monthly.	overall survival without tocilizumab failure was 0.81 [CI 95%; 0.7-0.95] at 12 months, 0.72 [CI 95%; 0.55-0.95] at 24 months and 0.48 [CI 95%; 0.2e-0.1] at 48 months

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86. In patients with active TAK, what is the impact of non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Flares	Aeshlimann, 2017	Comparative observational	At least 24 months	A total of 27 children with TAK (74% females) were included. Twenty-two children (81%) had evidence of active disease at diagnosis. The median age at diagnosis was 12.4 years (IQR 9.1–14.4).	4/27 children (15%) received high-dose corticosteroids only, and 18 (67%) received a combination of corticosteroids plus another immunosuppressive agent. These immunosuppressive agents prescribed in combination with cortico- steroids included MTX in ten (37%), cyclophosphamide in five (19%), and MTX plus a biologic agent in three (11%) children.	19 flares occurred during 44 non-biologic treatment episodes (43%) compared to only two flares during 12 biologic treatment episodes (17%). (p = 0.18; OR 3.80, 95% CI 0.81–18.59	Results reported for Biologics Vs non biologics, that is why it's not a comparative study, since GCs alone results are not presented
2-year flare-free survival	Aeshlimann, 2017	Comparative observational	At least 24 months	A total of 27 children with TAK (74% females) were included. Twenty-two children (81%) had evidence of	4/27 children (15%) received high-dose corticosteroids only, and 18 (67%) received a combination of corticosteroids plus another immunosuppressive agent. These	80% with biologic treatments compared to 43% in non-biologic treatments when adjusted for the number of treatment episodes	Results reported for Biologics Vs non biologics, that is why it's not a comparative study, since GCs alone results are not presented

				active disease at diagnosis. The median age at diagnosis was 12.4 years (IQR 9.1–14.4).	immunosuppressive agents prescribed in combination with cortico- steroids included MTX in ten (37%), cyclophosphamide in five (19%), and MTX plus a biologic agent in three (11%) children.	per patient (p = 0.03)	
Clinical Remission	Sun, 2017	Comparative observational	6 Months	Subjects included in this study met the following criteria: (i) active disease (Kerr score ≥ 2); (ii) no prior exposure to any immunosuppressants in the preceding 3 months; (iii) induction treatment was CYC plus GC or MTX plus GC.	CYC plus GC (N=39) or MTX plus GC (N=12).	The clinical remission rate was 71.7% (33/46) in the CYC group vs. 75% (9/12) in the MTX group.	
Disease activity through radiologic findings	Sun, 2017	Comparative observational	6 Months	Subjects included in this study met the following criteria: (i) active disease (Kerr score ≥ 2); (ii) no prior exposure	CYC plus GC (N=39) or MTX plus GC (N=12).	Radiologic assessment at the end of the 6-month induction revealed stable disease in 78.2% (36/46) and 83.3% (10/12) in	

				to any immunosuppressants in the preceding 3 months; (iii) induction treatment was CYC plus GC or MTX plus GC.		the CYC and MTX group, respectively.	
Side Effects	Sun, 2017	Comparative observational	6 Months	Subjects included in this study met the following criteria: (i) active disease (Kerr score ≥ 2); (ii) no prior exposure to any immunosuppressants in the preceding 3 months; (iii) induction treatment was CYC plus GC or MTX plus GC.	CYC plus GC (N=39) or MTX plus GC (N=12).	CYC group: menstrual disorders (17/46, 36.9%), gastrointestinal reaction (32/46, 69.6%,), myelosuppression (5/46, 10.9%), infection (4/46, 8.7%, pulmonary infection in three cases and urinary tract infection in 1) and malaise (9/46, 19.6%). Side effects in the MTX group included gastrointestinal reaction (5/12, 41.7%; loss of appetite in four cases and dental ulcer in 1), myelosuppression (1/12, 8.3%), liver dysfunction (2/12, 16.7%; alanine	

						aminotransferase ≤ 3 folds of the upper limit of normal), and trichomadesis (1/12; 8.3%).	

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

Author	Year	Title
Nakaoka	2017	Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study)
Aeshlimann	2017	Childhood Takayasu arteritis: disease course and response to therapy
Sun	2017	Cyclophosphamide could be a better choice than methotrexate as induction treatment for patients with more severe Takayasu's arteritis
Mekinian	2018	Efficacy of tocilizumab in Takayasu arteritis: Multicenter retrospective study of 46 patients

Takayasu Arteritis (TAK)

Treatment

- **PICO question 9:** In patients with active TAK, what is the impact of anti-TNF inhibitors + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Clinical symptoms, disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation

87. In patients with active TAK, what is the impact of anti-TNF inhibitors + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
No comparative data available

88. In patients with active TAK, what is the impact of anti-TNF inhibitors + glucocorticoid on disease-related outcomes and treatment-related adverse events?
No single arm data available

89. In patients with active TAK, what is the impact of non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
- **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Flares	Aeshlimann, 2017	Comparative observational	At least 24 months	A total of 27 children with TAK (74% females) were included. Twenty-two children (81%) had evidence of active disease at diagnosis. The median age at diagnosis was 12.4 years (IQR 9.1–14.4).	4/27 children (15%) received high-dose corticosteroids only, and 18 (67%) received a combination of corticosteroids plus another immunosuppressive agent. These immunosuppressive agents prescribed in combination with corticosteroids included MTX in ten (37%), cyclophosphamide in five (19%), and MTX plus a biologic agent in three (11%) children.	19 flares occurred during 44 non-biologic treatment episodes (43%) compared to only two flares during 12 bio-logic treatment episodes (17%). (p = 0.18; OR 3.80, 95% CI 0.81–18.59	Results reported for Biologics Vs non biologics, that is why it's not a comparative study, since GCs alone results are not presented

2-year flare-free survival	Aeshlimann, 2017	Comparative observational	At least 24 months	A total of 27 children with TAK (74% females) were included. Twenty-two children (81%) had evidence of active disease at diagnosis. The median age at diagnosis was 12.4 years (IQR 9.1–14.4).	4/27 children (15%) received high-dose corticosteroids only, and 18 (67%) received a combination of corticosteroids plus another immunosuppressive agent. These immunosuppressive agents prescribed in combination with corticosteroids included MTX in ten (37%), cyclophosphamide in five (19%), and MTX plus a biologic agent in three (11%) children.	80% with biologic treatments compared to 43% in non-biologic treatments when adjusted for the number of treatment episodes per patient (p = 0.03)	Results reported for Biologics Vs non biologics, that is why it's not a comparative study, since GCs alone results are not presented
Clinical Remission	Sun, 2017	Comparative observational	6 Months	Subjects included in this study met the following criteria: (i) active disease (Kerr score ≥ 2); (ii) no prior exposure to any immunosuppressants in the preceding 3 months; (iii) induction treatment was	CYC plus GC (N=39) or MTX plus GC (N=12).	The clinical remission rate was 71.7% (33/46) in the CYC group vs. 75% (9/12) in the MTX group.	

				CYC plus GC or MTX plus GC.			
Disease activity through radiologic findings	Sun, 2017	Comparative observational	6 Months	Subjects included in this study met the following criteria: (i) active disease (Kerr score ≥ 2); (ii) no prior exposure to any immunosuppressants in the preceding 3 months; (iii) induction treatment was CYC plus GC or MTX plus GC.	CYC plus GC (N=39) or MTX plus GC (N=12).	Radiologic assessment at the end of the 6-month induction revealed stable disease in 78.2% (36/46) and 83.3% (10/12) in the CYC and MTX group, respectively.	
Side Effects	Sun, 2017	Comparative observational	6 Months	Subjects included in this study met the following criteria: (i) active disease (Kerr score ≥ 2); (ii) no prior exposure to any immunosuppressants in the preceding 3 months; (iii) induction treatment was CYC plus GC or MTX plus GC.	CYC plus GC (N=39) or MTX plus GC (N=12).	CYC group: menstrual disorders (17/46, 36.9%), gastrointestinal reaction (32/46, 69.6%,), myelosuppression (5/46, 10.9%), infection (4/46, 8.7%, pulmonary infection in three cases and urinary tract infection in 1) and malaise (9/46, 19.6%). Side effects in the MTX group included gastrointestinal reaction (5/12, 41.7%;	

						loss of appetite in four cases and dental ulcer in 1), myelosuppression (1/12, 8.3%), liver dysfunction (2/12, 16.7%; alanine aminotransferase ≤ 3 folds of the upper limit of normal), and trichomadesis (1/12; 8.3%).	

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

Author	Year	Title
Aeshlimann	2017	Childhood Takayasu arteritis: disease course and response to therapy
Sun	2017	Cyclophosphamide could be a better choice than methotrexate as induction treatment for patients with more severe Takayasu's arteritis

Takayasu Arteritis (TAK)

Treatment

- **PICO question 10:** In patients with active TAK, what is the impact of abatacept + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Clinical symptoms, disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation

90. In patients with active TAK, what is the impact of abatacept + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No Comparative data available

91. In patients with active TAK, what is the impact of abatacept + glucocorticoid on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Number of Relapses	Langford, 2017	Randomized Controlled trial	40 months	34 eligible patients with TAK were enrolled	Treated with prednisone and abatacept; 26 reached the week 12 randomization and underwent a blinded randomization to abatacept or placebo.	The relapse-free survival at 12 months was 22% for those receiving abatacept and 40% for those receiving placebo (p= 0.853)
Number of serious Adverse Events	Langford, 2017	Randomized Controlled trial	40 months	34 eligible patients with TAK were enrolled	Treated with prednisone and abatacept; 26 reached the week 12 randomization and underwent a blinded randomization to abatacept or placebo.	There was no difference in the frequency or severity of adverse events between treatment arms, including infection. No deaths happened during the study.
Median duration of remission	Langford, 2017	Randomized Controlled trial	40 months	34 eligible patients with TAK were enrolled	Treated with prednisone and abatacept; 26 reached the week 12 randomization and underwent a blinded randomization to abatacept or placebo.	Treatment with abatacept in patients with TAK enrolled in this study was not associated with a longer median duration of remission (abatacept 5.5 months, placebo 5.7 months)

92. In patients with active TAK, what is the impact of non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
No single arm data available

References:

- Randomized controlled trials:
None

- Comparative observational studies:
None

- Single arm studies:

Author	Year	Title
Langford	2017	A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Takayasu Arteritis

Takayasu Arteritis (TAK)

Treatment

- **PICO question 11:** In patients with active TAK, what is the impact of rituximab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Clinical symptoms, disease activity, relapse, death, damage from disease, serious adverse events from medication (e.g., PML, hypogammaglobulinemia), infection, malignancy, toxicity leading to drug discontinuation

93. In patients with active TAK, what is the impact of rituximab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
No Comparative data available

94. In patients with active TAK, what is the impact of rituximab + glucocorticoid on disease-related outcomes and treatment-related adverse events?
No single arm data available

95. In patients with active TAK, what is the impact of non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
No single arm data available

References:

- Randomized controlled trials:
None

- Comparative observational studies:
None

- Single arm studies:
None

Takayasu Arteritis (TAK)

Treatment

- **PICO question 12:** In patients with active TAK, what is the impact of ustekinumab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Clinical symptoms, disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation

96. In patients with active TAK, what is the impact of ustekinumab + glucocorticoid vs. non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
No Comparative data available

97. In patients with active TAK, what is the impact of ustekinumab + glucocorticoid on disease-related outcomes and treatment-related adverse events?
No single arm data available

98. In patients with active TAK, what is the impact of non-glucocorticoid non-biologic immunosuppressive therapy + glucocorticoids on disease-related outcomes and treatment-related adverse events?
No single arm data available

References:

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

Takayasu Arteritis (TAK)

Treatment

- **PICO question 13:** In patients with active TAK, what is the impact of adding aspirin (any dose) or other anti-platelet therapy vs. not adding anti-platelet therapy on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Death, clinical symptoms from disease such as ischemia, damage from disease, serious adverse events from medication such as bleeding, toxicity leading to drug discontinuation

99. In patients with active TAK, what is the impact of adding aspirin (any dose) or other anti-platelet therapy vs. not adding anti-platelet therapy on disease-related outcomes and treatment-related adverse events?

100. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antiplatelet	no antiplatelet	Relative (95% CI)	Absolute (95% CI)		
Ischemic events												
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	-/0	-/0	HR 0.06 (0.05 to 0.51)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁◯◯ LOW	
Bleeding complications												
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	1/30 (3.3%)	0/18 (0.0%)	OR 1.88 (0.07 to 48.66)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations

a. Directly compares the interventions in which we are interested when applied to the populations in which we are interested and measures outcomes important to patients
b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

Author	Year	Title
De Souza	2010	Antiplatelet therapy for the prevention of arterial ischemic events in takayasu arteritis

- Comments:

Author	Year	Title	Comments
P. C. Grayson	2018	(18) F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis	Exclude. Antiplatelet therapy not used
R. Goel	2018	Long-term outcome of 251 patients with Takayasu arteritis on combination immunosuppressant therapy: Single centre experience from a large tertiary care teaching hospital in Southern India	Exclude. Antiplatelet therapy not used
K. M. Treitl	2017	3D-black-blood 3T-MRI for the diagnosis of thoracic large vessel vasculitis: A feasibility study	Exclude. Antiplatelet therapy not used
A. W. de Souza	2010	Antiplatelet therapy for the prevention of arterial ischemic events in takayasu arteritis	
M. Both	2008	MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis	Exclude. GCA imaging study. No TAK patient.

F. Numano	1986	Antiaggregative aspirin dosage at the affected vessel wall	Exclude. Biomarker study. Aspirin's platelet anti-aggregative studied by measurement of plasma prostanoid levels.
Ma Walter	2005	The value of FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease	Exclude. Imaging study. Had only 6 TAK patients. Antiplatelet therapy not used

Takayasu Arteritis (TAK)

Treatment

- **PICO question 14:** In patients with refractory TAK on glucocorticoid therapy, what is the impact of adding anti-TNF therapy vs. adding tocilizumab on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, toxicity leading to drug discontinuation

101. In patients with refractory TAK on glucocorticoid therapy, what is the impact of adding anti-TNF therapy vs. adding tocilizumab on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	TNF-A	Relative (95% CI)	Absolute (95% CI)		
Vascular signs - 6 months												
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	2/10 (20.0%)	6/32 (18.8%)	OR 1.08 (0.18 to 6.46)	**12 more per 1,000** (from 148 fewer to 411 more)	⨁◯◯◯ VERY LOW	
Constitutional signs - 3 months												
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	1/10 (10.0%)	3/33 (9.1%)	OR 1.11 (0.10 to 12.04)	**9 more per 1,000** (from 81 fewer to 455 more)	⨁◯◯◯ VERY LOW	
Complete response - 6 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	TNF-A	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	7/10 (70.0%)	17/32 (53.1%)	OR 2.06 (0.45 to 9.42)	**169 more per 1,000** (from 194 fewer to 383 more)	⨁◯◯◯ VERY LOW	
No response - 6 months												
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	1/10 (10.0%)	9/32 (28.1%)	OR 0.28 (0.03 to 2.58)	**183 fewer per 1,000** (from 270 fewer to 221 more)	⨁◯◯◯ VERY LOW	
Relapse free survival - 1 year												
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	6/14 (42.9%)	31/56 (55.4%)	OR 0.60 (0.19 to 1.97)	**127 fewer per 1,000** (from 363 fewer to 156 more)	⨁◯◯◯ VERY LOW	
Relapse free survival - 2 years												
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	1/14 (7.1%)	18/56 (32.1%)	OR 0.16 (0.02 to 1.34)	**251 fewer per 1,000** (from 312 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Relapse free survival - 3 years												
1	observational studies	not serious	not serious	not serious [a]	very serious [b]	none	1/14 (7.1%)	12/56 (21.4%)	OR 0.28 (0.03 to 2.38)	**143 fewer per 1,000** (from 206 fewer to 179 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Directly compares the interventions in which we are interested when applied to the populations in which we are interested and measures outcomes important to patients
b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision

102. In patients with refractory TAK on glucocorticoid therapy, what is the impact of adding anti-TNF therapy on disease-related outcomes and treatment-related adverse events?

- Patient important outcomes

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results
Remission – 2 studies with 22 patients with TAK with treatment with anti-TNF showed remission rates from 30-100% depending on definition.	Novikov, 2018	Retrospective, single center	Range 3-28 months, median 10 months	10 female patients with refractory TAK (ACR or Ishikawa); Prior to CZP administration, all patients received GC and MTX, CYC, AZA, HCQ, LEF or MMF. Six patients were also treated with bDMARD.	Certolizumab pegol (Anti-TNF). CZP was administered subcutaneously at a starting dosage of 400mg at weeks 0, 2 and 4. Subsequently, it was used at a standard dose of 200mg every 2 weeks	10/10 patients achieved remission. 7/10 patients had sustained remission of at least 4 months.
	Park, 2018	single-center open-label trial	54 weeks	12 patients with active TAK (all F, mean age 46.8y)	Infliximab biosimilar CT-P13 at a starting dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks up to week 46.	Partial or complete remission at week 30: three (27.3%) patients achieved complete remission and six (54.5%) patients achieved partial remission.
Infection – Two studies with 22 patients showed some infectious risk with anti-TNF treatment.	Novikov, 2018	Retrospective, single center	Range 3-28 months, median 10 months	10 female patients with refractory TAK (ACR or Ishikawa); Prior to CZP administration, all patients received GC and MTX, CYC, AZA, HCQ, LEF or MMF. Six patients were also treated with bDMARD.	Certolizumab pegol (Anti-TNF). CZP was administered subcutaneously at a starting dosage of 400mg at weeks 0, 2 and 4. Subsequently, it was used at a standard dose of 200mg every 2 weeks	2 with mild herpes labialis, 1 with community acquired pneumonia, 1 with tonsillitis, 1 with UTI
	Park, 2018	single-center open-label trial	54 weeks	12 patients with active TAK (all F, mean age 46.8y)	Infliximab biosimilar CT-P13 at a starting dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks up to week 46.	4 (33.3%) had infection (URI, Viral keratitis were reported).
Side effects requiring discontinuation of drug – In one study of 12 patients showed no side effects requiring discontinuation over study period.	Park, 2018	single-center open-label trial	54 weeks	12 patients with active TAK (all F, mean age 46.8y)	Infliximab biosimilar CT-P13 at a starting dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks up to week 46.	During the treatment period, there were no serious adverse events (SAEs) or AEs necessitating discontinuation of CT-P13.

103. In patients with refractory TAK on glucocorticoid therapy, what is the impact of adding tocilizumab on disease-related outcomes and treatment-related adverse events?

- Patient important outcomes

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results

Treatment Response n- One study with 46 patients showed two thirds of patient will have a treatment response.	Mekinian, 2018	Retrospective multicenter study	36 months	46 patients with TAK (median age 43; 35F)	Tocilizumab. Tocilizumab was mainly used intravenously at 8 mg/kg monthly.	12/36 (67%) had a treatment response.
Side effect requiring drug discontinuation – In 1 study of 46 patients, 2 patients had to discontinue treatment with TZ due to side effects.	Mekinian, 2018	Retrospective multicenter study	36 months	46 patients with TAK (median age 43; 35F)	Tocilizumab. Tocilizumab was mainly used intravenously at 8 mg/kg monthly.	Two (4%) cases required treatment discontinuation, including neoplasm and one severe asymptomatic neutropenia.
Survival – In one study of 46 patients, rate of three-quarters of patients were still on drug at two years without event.	Mekinian, 2018	Retrospective multicenter study	3 years	46 patients with TAK (median age 43; 35F)	Tocilizumab. Tocilizumab was mainly used intravenously at 8 mg/kg monthly.	overall survival without tocilizumab failure was 0.81 [CI 95%; 0.7-0.95] at 12 months, 0.72 [CI 95%; 0.55-0.95] at 24 months and 0.48 [CI 95%; 0.2e-0.1] at 48 months
Relapse – One stdy of 46 patients showed relapse rate of 6 percent, which was lower than just DMARDs in the study.	Mekinian, 2018	Retrospective multicenter study	3 years	46 patients with TAK (median age 43; 35F)	Tocilizumab. Tocilizumab was mainly used intravenously at 8 mg/kg monthly.	The cumulative incidence of relapse was significantly higher under DMARDs therapy compared to tocilizumab (34.6% vs 6.3%; p = 0.049, respectively)

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

Author	Year	Title
A. Mekinian, C. Comarmond	2015	Efficacy of Biological-Targeted Treatments in Takayasu Arteritis: Multicenter, Retrospective Study of 49 Patients

- Single arm studies:

Author	Year	Title
Novikov	2018	Certolizumab pegol in the treatment of Takayasu arteritis
Park	2018	Infliximab biosimilar CT-P13 therapy in patients with Takayasu arteritis with low dose of glucocorticoids: a prospective single-arm study

Mekinian	2018	Efficacy of tocilizumab in Takayasu arteritis: Multicenter retrospective study of 46 patients

Takayasu Arteritis (TAK)

Treatment

- **PICO question 15:** In patients with TAK who achieved remission on glucocorticoids, what is the impact of low dose maintenance glucocorticoids vs. no maintenance glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease activity, relapse, death, damage from disease, clinical symptoms, patient reported outcomes, infection, toxicity leading to drug discontinuation

104. In patients with TAK who achieved remission on glucocorticoids, what is the impact of low dose maintenance glucocorticoids vs. no maintenance glucocorticoids on disease-related outcomes and treatment-related adverse events?
No comparative data available

105. In In patients with TAK who achieved remission on glucocorticoids, what is the impact of low dose maintenance glucocorticoids on disease-related outcomes and treatment-related adverse events?
No single arm data available

106. In In patients with TAK who achieved remission on glucocorticoids, what is the impact of no maintenance glucocorticoids on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

- Comments:

Author	Year	Title	Comments
Y. Sun	2018	Analysis of predictive factors for treatment resistance and disease relapse in Takayasu's arteritis	Exclude. Does not address any arm of PICO question
F. A. Aeschlimann	2017	Childhood Takayasu arteritis: disease course and response to therapy	Exclude. Only one patient was on maintenance low dose prednisone. More appropriate for PICO 7 and 8
R. Goel	2018	Long-term outcome of 251 patients with Takayasu arteritis on combination immunosuppressant therapy: Single centre experience from a large tertiary care teaching hospital in Southern India	Exclude. Majority of patients received steroid sparing immunosuppressive agents for maintenance. Did not present outcome of patients on steroid monotherapy
S. Fukui	2016	Fewer subsequent relapses and lower levels of IL-17 in Takayasu arteritis developed after the age of 40 years	Exclude. Does not address PICO question
A. Fraga	1972	Takayasu's arteritis: frequency of systemic manifestations (study of 22 patients) and favorable response to maintenance steroid therapy with adrenocorticosteroids (12 patients)	Exclude. While low dose prednisone was used for maintenance, the data quality is low (just reported frequency of improved symptoms, table 5). No relevant informative outcome data can be obtained.

Takayasu Arteritis (TAK)

Treatment

- **PICO question 16:** In patients with TAK with asymptomatic progression of a previously identified vascular lesion, what is the impact of escalating or changing immunosuppression vs. continuing current therapy on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation

107. In patients with TAK with asymptomatic progression of a previously identified vascular lesion, what is the impact of escalating or changing immunosuppression vs. continuing current therapy on disease-related outcomes and treatment-related adverse events?
No comparative data available

108. In patients with TAK with asymptomatic progression of a previously identified vascular lesion, what is the impact of escalating or changing immunosuppression on disease-related outcomes and treatment-related adverse events?
No single arm data available

109. In patients with TAK with asymptomatic progression of a previously identified vascular lesion, what is the impact of continuing current therapy on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies :
  None

- Comments:

Author	Year	Title	Comments
Y. Sun	2018	Analysis of predictive factors for treatment resistance and disease relapse in Takayasu's arteritis	Excluded. This study did not identify TAK patients with asymptomatic progression of previously identified vascular lesions.

Takayasu Arteritis (TAK)

Treatment

- **PICO question 17:** In patients with known TAK who develop a new vascular lesion in a previously unaffected vascular territory, what is the impact of escalating or changing immunosuppression vs. continuing current therapy on disease-related outcomes and treatment-related adverse events?
- **Critical Outcomes:** Disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation

110. In patients with known TAK who develop a new vascular lesion in a previously unaffected vascular territory, what is the impact of escalating or changing immunosuppression vs. continuing current therapy on disease-related outcomes and treatment-related adverse events?
No comparative data available

111. In patients with known TAK who develop a new vascular lesion in a previously unaffected vascular territory, what is the impact of escalating or changing immunosuppression on disease-related outcomes and treatment-related adverse events?

- **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Restenosis-free survival rates	Gulcu, 2017	Retrospective case-series study	1 and 8 years	35 patients (median age: 45 years, range: 22-77 years) with 49 stenotic arterial lesions caused by TA who underwent endovascular treatment	GC treatment (20-30 mg/day) after endovascular intervention. High dose of prednisolone (0.8-1 mg/kg) was given when systemic symptoms of inflammation.	4 (8%) lesions were occluded or showed restenosis. 1- and 8-year restenosis-free survival rates of renal artery interventions were 74% and 57% (P = 0.281)
Adverse events	Gulcu, 2017	Retrospective case-series study	1 and 8 years	35 patients (median age: 45 years, range: 22-77 years) with 49 stenotic arterial lesions caused by TA who underwent endovascular treatment	GC treatment (20-30 mg/day) after endovascular intervention. High dose of prednisolone (0.8-1 mg/kg) was given when systemic symptoms of inflammation.	Other than the 3 occluded lesions, No symptoms in the remaining 45 (92%) lesions.

112. In patients with known TAK who develop a new vascular lesion in a previously unaffected vascular territory, what is the impact of continuing current therapy on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None
- Comparative observational studies:

None

- Single arm studies:

Author	Year	Title
Gulcu	2017	Long-Term Follow-Up of Endovascular Repair in the Management of Arterial Stenosis Caused by Takayasu's Arteritis

- Comments: The study does not specify the treatment received before intervention, but since patients received high dose GCs, we assume that the regimen was escalated.

Takayasu Arteritis (TAK)

Treatment

- **PICO question 18:** In patients with TAK in apparent clinical remission but with signs of active large vessel vascular inflammation on non-invasive imaging, what is the impact of treating with immunosuppressive therapy vs. not treating with immunosuppressive therapy on disease-related outcomes or treatment related adverse events?

- **Critical Outcomes:** Disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation

113. In patients with TAK in apparent clinical remission but with signs of active large vessel vascular inflammation on non-invasive imaging, what is the impact of treating with immunosuppressive therapy vs. not treating with immunosuppressive therapy on disease-related outcomes or treatment related adverse events?
No Comparative data available

114. In patients with TAK in apparent clinical remission but with signs of active large vessel vascular inflammation on non-invasive imaging, what is the impact of treating with immunosuppressive therapy on disease-related outcomes or treatment related adverse events?
No single arm data available

115. In patients with TAK in apparent clinical remission but with signs of active large vessel vascular inflammation on non-invasive imaging, what is the impact of not treating with immunosuppressive therapy on disease-related outcomes or treatment related adverse events?
No single arm data available

References:

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

Takayasu Arteritis (TAK)

Treatment

- **PICO question 19:** In patients with TAK in apparent clinical remission but with rising inflammatory markers, what is the impact of continued clinical observation without escalation of immunosuppression versus escalating immunosuppression on disease-related outcomes, and treatment-related adverse events?

- **Critical Outcomes:** Clinical symptoms, disease activity, relapse, death, damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation

116. In patients with TAK in apparent clinical remission but with rising inflammatory markers, what is the impact of continued clinical observation without escalation of immunosuppression versus escalating immunosuppression on disease-related outcomes, and treatment-related adverse events?
  No Comparative data available

117. In patients with TAK in apparent clinical remission but with rising inflammatory markers, what is the impact of continued clinical observation without escalation of immunosuppression on disease-related outcomes, and treatment-related adverse events?
  No single arm data available

118. In patients with TAK in apparent clinical remission but with rising inflammatory markers, what is the impact of escalating immunosuppression on disease-related outcomes, and treatment-related adverse events?
  No single arm data available

References:

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

Takayasu Arteritis (TAK)

Surgical Intervention

- **PICO question 20:** In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, what is the impact of surgical intervention with continued immunosuppression vs. continued immunosuppression alone on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?

- **Critical Outcomes:** Serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation, ischemic events, complications of the intervention such as bleeding or thrombotic events, death

1. In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, what is the impact of surgical intervention with continued immunosuppression vs. continued immunosuppression alone on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
   No comparative data available

2. In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, what is the impact of surgical intervention with continued immunosuppression on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
   - **Patient important outcome:**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Relapse-free	Zheng, 2018	Retrospective case-series	Mean (SD) 2.1 (0.6) years	46 TA patients with lesions	All 46 patients underwent surgery or angioplasty. 24 patients were treated with corticosteroid and/or immunosuppressive drugs before surgery.	23/46 (50%) of patients treated with GC/IS prior to surgery had no complication or death
Patency	Pajari, 1986	Retrospective case-series	Up to 15 years	29 patients TA with lesions	The 29 patients underwent 49 vascular procedures due to arterial insufficiency. Patency was evaluated in 35 grafts (17 with patients in	5-year patency rate after grats in patients with inactive disease stage was 88% +/- 8%

					active disease and 18 in patients with inactive disease).	
Complications	Zheng, 2018	Retrospective case-series	Mean (SD) 2.1 (0.6) years	46 TA patients with lesions	All 46 patients underwent surgery or angioplasty. 24 patients were treated with corticosteroid and/or immunosuppressive drugs before surgery.	1/46 (2%) of patients treated with GC/IS prior to surgery had a complication

3. In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, what is the impact of surgical intervention with continued immunosuppression alone on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
   No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:

Author	Year	Title
Zheng	2018	Treatment with Corticosteroid and/or Immunosuppressive Agents before Surgery can Effectively Improve the Surgical Outcome in Patients with Takayasu's Arteritis
Pajari	1986	Treatment of Takayasu's arteritis: an analysis of 29 operated patients

- Studies reviewed and excluded:

Author	Year	Title	Comments
X. L. Cong	2010	Takayasu's arteritis: clinical features and outcomes of 125 patients in China	Thirteen of the 20 patients had active disease and received strict perioperative GC during vascular procedures. Exclude
S. Tyagi	1999	Percutaneous transluminal angioplasty for stenosis of the aorta due to aortic arteritis in children	9/41 had active disease and were the only ones who received immunosuppression, the data isn't presented for the 32 patients without GCs as well, so the population is not relevant to the question - Exclude

S. Joseph	1994	Percutaneous transluminal angioplasty of the subclavian artery in nonspecific aortoarteritis: results of long-term follow-up	by definition of active disease, most patients had active disease by the time of the intervention, and no immunosuppression was mentioned to be given with the surgical intervention - Exclude
S. A. Rao	1993	Takayasu arteritis: initial and long-term follow-up in 16 patients after percutaneous transluminal angioplasty of the descending thoracic and abdominal aorta	Patients with active disease by definition - Exclude
M. Okita	2000	Evaluation of the results of surgical treatment for dilative lesions associated with Takayasu's arteritis	Patients don't have inactive disease with limb claudication - Exclude

Takayasu Arteritis (TAK)

Surgical Intervention

- **PICO question 21:** In patients with known TAK with worsening signs of limb/organ ischemia on immunosuppression, what is the impact of surgical intervention with escalating immunosuppression vs. escalating immunosuppression alone on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?

- **Critical Outcomes:** Damage from disease, disease activity, relapse, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation, ischemic events, complications of the intervention such as bleeding or thrombotic events, death

119. In patients with known TAK with worsening signs of limb/organ ischemia on immunosuppression, what is the impact of surgical intervention with escalating immunosuppression vs. escalating immunosuppression alone on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
    - No data available

120. In patients with known TAK with worsening signs of limb/organ ischemia on immunosuppression, what is the impact of surgical intervention with escalating immunosuppression on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
    - **Patient Important Outcomes:**

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

Survival rate & Death	Ando, 2000	Case-series	Follow-up from 1 to 246 months (mean, 107 months)	87 patients with TA. 43 cases of thoracic aortic aneurysm (TAA) and 44 cases of diffuse dilatation of the ascending aorta with aortic regurgitation (AR).	Artificial graft for TAA, valve replacement for AR. Preoperative GC administered to 40 patients with high CRP and ESR.	Cumulative survival rates of 87 patients with Takayasu arteritis complicated by dilative lesions were as follows: 87.6% after 3 years, 79.7% after 6 years, and 74.3% after 9 years. 5 patients (5.7%) died during the hospital stay. 15 patients of late deaths, and 10 patients died due to cardiovascular problems. Hospital Death: TAA Group: 43 Patients Hospital Death: 2 Patients (4.7%) Late Death: 7 On Steroids: 12 Patients (28%) Dilation of Aorta: 44 Patients Hospital Death: 3 (6.8%) Late Death: 8 On Steroids: 28 Patients (64%)
Patency & Restenosis	Yildyz, 2014	Case-series	6 months	24 patients with TA	Percutaneous intervention, surgical and medical treatments. Immunosuppressive therapy including steroids and/or methotrexate, azathioprine and cyclophosphamide before percutaneous intervention.	At 6 months follow-up, the arteries were patent and showed no proliferative lesions in 8 patients. Restenosis 1/24 (4%).
Recurrence – one study with 65 patients showed no difference in symptomatic (or radiographic) recurrence with respect to disease activity status.	Lee, 2014	Retrospective single center cohort study	2 years	65/235 (27.7%) patients with TAK (ACR criteria) 1994-2011 underwent arterial revascularization for 111 arterial lesions	45 lesions with surgical bypass 66 lesions with PTA Variable assessed was disease activity's effect on outcomes. If active the patient was given moderate to high doses of prednisone perioperatively If inactive, no prednisone was given or increased, and patient continued on their own IS regimen	There were no statistically significant differences in symptomatic recurrence between clinically active TA under immunosuppression and clinically inactive TA without additional immunosuppression during the peri-procedural period ($p = 0.30$).The results were similar when the symptomatic recurrence free survivals for each revascularization method were examined. In the 64 lesions treated by PTA, symptomatic recurrence was not significantly different according to the need for additional immunosuppressive therapy during the peri-procedural period ($p = 0.20$), no specific numbers presented

121. In patients with known TAK with worsening signs of limb/organ ischemia on immunosuppression, what is the impact of escalating immunosuppression alone on the development of disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?

- **Patient Important Outcomes:**

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Remission	Vinicki, 2017	Retrospective case-series	6 months	5 patients with TA, and 5 patients with GCA, refractory to conventional therapies including GC.	All patients received either infliximab (IFX), etanercept (ETN) or tocilizumab (TCZ), 4/5 TA patients received less than 10 mg/day of prednisone.	Only 5 patients with TA Remission in all patients. Sustained remission in all cases during follow up (mean follow-up 59.6 ± 27.2 months).
	Henes, 2011	Retrospective case-series	Median follow-up of 45 months	10 patients with LLV	CYC plus GC	Complete remission in all patients by end of follow-up
SAE	Henes, 2011	Retrospective case-series	Median follow-up of 45 months	10 patients with LLV	CYC plus GC	SAE – 6 (60%); streptococcus mitis sepsis, reactivation of PJP (pneumocystis jirovecii pneumonia)
Adverse events	Vinicki, 2017	Retrospective case-series	6 months	5 patients with TA, and 5 patients with GCA, refractory to conventional therapies including GC.	All patients received either infliximab (IFX), etanercept (ETN) or tocilizumab (TCZ), 4/5 TA patients received less than 10 mg/day of prednisone.	None of the patients developed a new arterial lesion. Recurrent infection in 1 patient. Neutropenia in 1 patient.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

Author	Year	Title
Vinicki	2017	Sustained remission after long-term biological therapy in patients with large vessel vasculitis: an analysis of ten cases
Henes	2011	Cyclophosphamide for large vessel vasculitis: assessment of response by PET/CT
Yildyz	2014	Outcomes and effectiveness of percutaneous intervention in patients with takayasu's arteritis
Ando	2000	Evaluation of the results of surgical treatment for dilative lesions associated with Takayasu's arteritis
Lee	2014	Comparison of outcomes between endovascular treatment and bypass surgery in Takayasu arteritis

Takayasu Arteritis (TAK)

Surgical Intervention

- **PICO question 16:** In patients with TAK with stenosis of a cranial/cervical vessel without clinical symptoms, what is the impact of surgical intervention combined with continued immunosuppression vs. continued immunosuppression alone on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?

- **Critical outcomes:** Damage from disease, serious adverse events from medication, infection, malignancy, toxicity leading to drug discontinuation, ischemic events, complications of the intervention such as bleeding or thrombotic events, death

122. In patients with TAK with stenosis of a cranial/cervical vessel without clinical symptoms, what is the impact of surgical intervention combined with continued immunosuppression vs. continued immunosuppression alone on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
    - No comparative data available

123. In patients with TAK with stenosis of a cranial/cervical vessel without clinical symptoms, what is the impact of surgical intervention combined with continued immunosuppression on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
    - **Patient Important Outcomes**

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results	Comments

Technical success 2 studies reported the rate of successful operations that ranged from 83% to 92.3%.	Kim, 2011	Retrospective case-series	Mean clinical follow-up duration 39 months (range 11-91 months)	12 patients with TA	Percutaneous transluminal balloon angioplasty (PTA) and/or stenting. Prednisolone (1 mg/kg/d) and methotrexate (7.5 mg/wk) in patients unresponsive to steroids.	Technical success: 20 procedures in 11 patients (92%) One procedure failed with 50% residual stenosis.	Indirect; All patients presented with symptoms. of the 12 included patients, five had ischemic stroke, three had tIA (transient hemiparesis, aphasia, or visual loss), three had dizziness and one had decreased vision; Prednisolone administered to patients with increased ESR before endovascular treatment.
	Cong, 2010	Retrospective case-series	Median duration of 36 months (3–180 months)	80 patients diagnosed with TA, mean age 26.9 years (6–65 years).	20 patients received angioplasty procedures. Vascular bypass in 36 patients. 23 of them received perioperative GC, 13 preventive GC. GC in 58 patients (72.5%). 16 patients on DMARDs in addition to GC.	1) Vascular bypass + GC patients: 30/36 (83%) 2) Angioplasty procedures: 22/25 (88%) initially successful with or without stents.	Indirect; Data not separated for stable disease. Combined with patients that have active disease. Does not separate patient outcomes/ lesion location.
Restenosis Reported by 2 studies that had inconsistent rates 10% and 77.3%.	Kim, 2011	Retrospective case-series	Mean clinical follow-up duration 39 months (range 11-91 months)	12 patients with TA	Percutaneous transluminal balloon angioplasty (PTA) and/or stenting. Prednisolone (1 mg/kg/d) and methotrexate (7.5 mg/wk) in patients unresponsive to steroids.	Restenosis in 2/10 patients (10%) without symptom recurrence.	Indirect; All patients presented with symptoms. of the 12 included patients, five had ischemic stroke, three had tIA (transient hemiparesis, aphasia, or visual loss), three had dizziness and one had decreased vision
	Cong, 2010	Retrospective case-series	Median duration of 36 months (3–180 months)	80 patients diagnosed with TA, mean age 26.9 years (6–65 years).	20 patients received angioplasty procedures. Vascular bypass in 36 patients. 23 of them received perioperative GC, 13 preventive GC. GC in 58 patients (72.5%). 16 patients on DMARDs in addition to GC.	Restenosis in 17/22 (77.3%). 14 of the 17 (82.4%) developed in less than 1 year.	Indirect; Data not separated for stable disease. Combined with patients that have active disease. Does not separate patient outcomes/ lesion location.

Remission Reported by 2 studies; Remission 67-68%	Cong, 2010	Retrospective case-series	Median duration of 36 months (3–180 months)	80 patients diagnosed with TA, mean age 26.9 years (6–65 years).	20 patients received angioplasty procedures. Vascular bypass in 36 patients. 23 of them received perioperative GC, 13 preventive GC. GC in 58 patients (72.5%). 16 patients on DMARDs in addition to GC.	Postoperative remission in 23 (67.65%) patients on GC prior to surgery. Relapse-free 5/16 patients treated with a combination of DMARD and GC.	Indirect; Data not separated for stable disease. Combined with patients that have active disease. Does not separate patient outcomes/ lesion location.
	Zheng, 2018	Retrospective case-series	Mean (SD) 2.1 (0.6) years	46 TA patients with lesions	All 46 patients underwent surgery or angioplasty. 24 patients were treated with corticosteroid and/or immunosuppressive drugs before surgery.	34(68%) of patients with relief treated with GC/IS prior to surgery.	Indirect evidence; 34 had active disease prior to surgery; outcome data not separated for active and inactive disease.
Complications Reported by 4 studies; all indirect evidence/ postoperative complications ranges from 8-22%	Zheng, 2018	Retrospective case-series	Mean (SD) 2.1 (0.6) years	46 TA patients with lesions	All 46 patients underwent surgery or angioplasty. 24 patients were treated with corticosteroid and/or immunosuppressive drugs before surgery.	1/12 (8%) of patients with complications treated with GC/IS.	Indirect evidence; outcome data not separated for active and inactive disease.
	Singh, 2015	Retrospective case-series		62 patients with TA with various angiographic involvement; 10 TA with cervicocranial involvement; LCCA [3], RCCA [2] ;LSCA [5]	23 patients went balloon angioplasty and prednisone 1mg/kg/day or/and MTX 7.5-15mg/week prior to and after surgery	1/3 LCCA Cerebral Infarction 1/2 Cerebral Infarction	Indirect evidence; all patients have symptoms; LUL calud, vertigo; blurring of eye.
	Kim, 2011	Retrospective case-series	Mean clinical follow-up duration 39 months (range 11-91 months)	12 patients with TA	Percutaneous transluminal balloon angioplasty (PTA) and/or stenting. Prednisolone (1 mg/kg/d) and methotrexate (7.5 mg/wk) in patients unresponsive to steroids.	Occlusion occurred in one patient. One patient had a minor stroke three months later.	Indirect; All patients presented with symptoms. of the 12 included patients, five had ischemic stroke, three had tIA (transient hemiparesis, aphasia, or visual loss), three had dizziness and one had decreased vision

	Cong, 2010	Retrospective case-series	Median duration of 36 months (3–180 months)	80 patients diagnosed with TA, mean age 26.9 years (6–65 years).	20 patients received angioplasty procedures. Vascular bypass in 36 patients. 23 of them received perioperative GC, 13 preventive GC. GC in 58 patients (72.5%). 16 patients on DMARDs in addition to GC.	Postoperative complications in 4/36 (22%) Angioplasty procedures: 3 unsuccessful.	Indirect; Data not separated for stable disease. Combined with patients that have active disease. Does not separate patient outcomes/ lesion location.
Death Death was reported in 8 studies ranged from 2% to 11%.	Zheng, 2018	Retrospective case-series	Mean (SD) 2.1 (0.6) years	46 TA patients with lesions	All 46 patients underwent surgery or angioplasty. 24 patients were treated with corticosteroid and/or immunosuppressive drugs before surgery.	1 (2.2%) death as a result of perioperative complication.	Indirect evidence; outcome data not separated for active and inactive disease.
	Singh, 2015	Retrospective case-series		62 patients with TA with various angiographic involvement; 10 TA with cervicocranial involvement; LCCA [3], RCCA [2] ;LSCA [5]	23 patients went balloon angioplasty and prednisone 1mg/kg/day or/and MTX 7.5-15mg/week prior to and after surgery	1/10 or 1/3 LCCA TA patients with cervicocranial involvement died from infarction.	Indirect evidence; all patients have symptoms; LUL calud, vertigo; blurring of eye.
	Kim, 2011	Retrospective case-series	Mean clinical follow-up duration 39 months (range 11-91 months)	12 patients with TA	Percutaneous transluminal balloon angioplasty (PTA) and/or stenting. Prednisolone (1 mg/kg/d) and methotrexate (7.5 mg/wk) in patients unresponsive to steroids.	One patient died from cardiac failure 36 months after successful angioplasty (8%).	Indirect; All patients presented with symptoms. of the 12 included patients, five had ischemic stroke, three had tIA (transient hemiparesis, aphasia, or visual loss), three had dizziness and one had decreased vision
	Cong, 2010	Retrospective case-series	Median duration of 36 months (3–180 months)	80 patients diagnosed with TA, mean age 26.9 years (6–65 years).	20 patients received angioplasty procedures. Vascular bypass in 36 patients. 23 of them received perioperative GC, 13 preventive GC. GC in 58 patients (72.5%). 16 patients on DMARDs in addition to GC.	Vascular bypass + GC patients: 2/36 (6%) vascular bypass patients died.	Indirect; Data not separated for stable disease. Combined with patients that have active disease. Does not separate patient outcomes/ lesion location.

	Ando, 2000	Retrospective case-series 13 patients with occlusive cervical vessel lesions.	Follow-up ranged from 1 to 240 months (mean: 117 months).	46 TA patients with coronary and aortic stenosis.	Transaortic ostial endarterectomy (TAE) in 9, coronary artery bypass grafting (CABG) in 10, 4 patients TAE and valve replacement. Preoperative steroids to 22 patients.	Death: 5/46 (11%)	Indirect; unclear if patients had symptoms.
	Ando, 2000	Case-series	Follow-up from 1 to 246 months (mean, 107 months)	87 patients with TA. 43 cases of thoracic aortic aneurysm (TAA) and 44 cases of diffuse dilatation of the ascending aorta with aortic regurgitation (AR).	Artificial graft for TAA, valve replacement for AR. Preoperative GC administered to 40 patients with high CRP and ESR.	5 patients (5.7%) died during the hospital stay. 15 patients of late deaths, and 10 patients died due to cardiovascular problems. The total actuarial survival rate was 79.7% at 6 years and 74.3% at 9 years.	Indirect; no patient presentations/symptoms available.
	Han, 2017	Retrospective Cohort	61 months, mean	19 patients with Takayasu arteritis who underwent aorto-carotid bypass from March 2002 to April 2015	Eleven patients (57.9%) underwent aorto-uni-carotid bypass and 8 patients (42.1%) underwent aorto-bi-carotid bypass. Surgery was done after normalization of ESR and CRP level by using steroids and immunosuppressants like prednisolone or methylprednisolone.	3/19 died during followup (2 were less than 3 years)	Indirect – These patients were symptomatic.
	Robbs, 1994	Single Center Cohort, retrospective	3mo to 11 y	1981 and March 1993, 134 patients with a clinical diagnosis of Takayasu's Arteritis were referred to the Vascular Service for consideration for operative therapy.	Eighty-one patients (60%) were deemed suitable for reconstructive surgery and submitted to operation. 22/81 had renovascular HTN.	Overall operative mortality in the Type I patients was 3.6% (stroke) and in the type II-IV **4%.**	Indirect - These patients were symptomatic. Data here is for all-comers

124. In patients with TAK with stenosis of a cranial/cervical vessel without clinical symptoms, what is the impact of continued immunosuppression alone on disease-related outcomes, treatment-related adverse events, and surgical intervention-related adverse events?
   - No available data.

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies :

Author	Year	Title
Ando, M	2000	Surgical considerations of occlusive lesions associated with Takayasu's arteritis
Ando, M	2000	Evaluation of the results of surgical treatment for dilative lesions associated with Takayasu's arteritis
Cong, X	2010	Takayasu's arteritis: clinical features and outcomes of 125 patients in China
Kim, H	2011	Outcomes after endovascular treatment of symptomatic patients with Takayasu's arteritis
Singh, A	2015	Angiographic profile and endovascular interventions in Takayasu's arteritis
Zheng, T	2018	Treatment with Corticosteroid and/or Immunosuppressive Agents before Surgery can Effectively Improve the Surgical Outcome in Patients with Takayasu's Arteritis
Han	2017	Aorto-carotid bypass in patients with Takayasu arteritis
Robbs	1994	Arterial reconstruction for non-specific arteritis (Takayasu's disease): medium to long term results

- Studies reviewed and excluded:

Author	Year	Title	Comments
J. P. Vinicki	2017	Sustained remission after long-term biological therapy in patients with large vessel vasculitis: an analysis of ten cases	Less than 10 patients with TA. Exclude
J. Loricera	2014	Tocilizumab in refractory aortitis: study on 16 patients and literature review	Less than 10 patients with TA. Exclude

- **PICO question 23:** In patients with TAK with worsening signs of limb/organ ischemia, what is the impact of performing surgical intervention while the patient has active disease versus delaying until the disease is in remission on disease-related outcomes and surgical intervention-related adverse events?

- **Critical Outcomes:** Damage from disease, clinical symptoms from disease, disease activity, relapse, infection, ischemic events, complications of the intervention such as bleeding or thrombotic events, need for additional intervention or immunosuppression, death

125. In patients with TAK with worsening signs of limb/organ ischemia, what is the impact of performing surgical intervention while the patient has active disease versus delaying until the disease is in remission on disease-related outcomes and surgical intervention-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quiescent	Active Disease	Relative (95% CI)	Absolute (95% CI)	
5 year freedom from revision											
1 [1]	observational studies	not serious	not serious	not serious	very serious [1,a]	none	28/29 (96.6%)	6/13 (46.2%)	OR 32.67 (3.36 to 317.22)	**504 more per 1,000** (from 281 more to 535 more)	⨁◯◯◯ VERY LOW
10 year freedom from revision											
1 [1]	observational studies	not serious	not serious	not serious	very serious [1,a]	none	24/29 (82.8%)	6/13 (46.2%)	OR 5.60 (1.31 to 24.00)	**366 more per 1,000** (from 67 more to 492 more)	⨁◯◯◯ VERY LOW
Freedom from graft revision or progression of disease											
1 [1]	observational studies	not serious	not serious	not serious	very serious [1,a]	none	27/29 (93.1%)	5/13 (38.5%)	OR 21.60 (3.50 to 133.28)	**546 more per 1,000** (from 302 more to 604 more)	⨁◯◯◯ VERY LOW
Restenosis rate											
1 [3]	observational studies	not serious [b]	not serious	not serious	not serious	none	3/25 (12.0%)	17/38 (44.7%)	OR 0.17 (0.04 to 0.66)	**326 fewer per 1,000** (from 416 fewer to 99 fewer)	⨁⨁◯◯ LOW
MACE in patients with coronary artery intervention											
1 [2]	observational studies	very serious [2,b,c]	not serious	not serious	very serious [2,a]	none	2 participants	22 participants	HR 10.58 (2.35 to 47.59)	**-- per 100** (from -- to --)	

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quiescent	Active Disease	Relative (95% CI)	Absolute (95% CI)	
									[MACE in patients with coronary artery intervention]	-- **per 100** (from -- to --)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

Explanations

a. Clinical action may differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision.
b. High risk of bias for selection of intervention group and control group
c. Median follow-up time was significantly shorter for PCI group compared to CABG group; Difference in included PCI and CABG groups; CABG group had fewer women and more current or past smokers.

References

1. Fields, C.,E., Bower, T.,C., Cooper, L.,T., Hoskin, T., Noel, A.,A., Panneton, J.,M., Sullivan, T.,M., Gloviczki, P., Cherry, K.,J. Takayasu's arteritis: operative results and influence of disease activity. J Vasc Surg; 2006.
2. Wang, X., Dang, A., Lv, N., Cheng, N., Cheng, X., Yang, Y., Song, Y. Long-term outcomes of coronary artery bypass grafting versus percutaneous coronary intervention for Takayasu arteritis patients with coronary artery involvement. Seminars in Arthritis and Rheumatism; 2017.
3. M. C. Park, S. W. Lee, Y. B. Park, S. K. Lee, D. Choi, W. H. Shim. Post-interventional immunosuppressive treatment and vascular restenosis in Takayasu's arteritis. Rheumatology 2006

- **References:**

- Randomized controlled trials: None
  - Comparative observational studies:

Author	Year	Title
Fields, C	2006	Takayasu's arteritis: operative results and influence of disease activity
Park, M	2006	Post-interventional immunosuppressive treatment and vascular restenosis in Takayasu's arteritis
Wang, X	2017	Long-term outcomes of coronary artery bypass grafting versus percutaneous coronary intervention for Takayasu arteritis patients with coronary artery involvement.

Takayasu Arteritis (TAK)

Surgical Intervention

- **PICO question 18:** In patients with TAK with worsening signs of limb/organ ischemia, what is the impact of endovascular interventions (such as angioplasty or stent placement) versus vascular bypass or grafting on disease-related outcomes and surgical treatment-related adverse events?

- **Critical Outcomes**: Damage from disease, infection, ischemic events, complications of the intervention such as bleeding or thrombotic events, adverse reaction to contrast exposure, need for additional intervention, death

126. In patients with TAK with worsening signs of limb/organ ischemia, what is the impact of endovascular interventions (such as angioplasty or stent placement) versus vascular bypass or grafting on disease-related outcomes and surgical treatment-related adverse events?

Subgroup 1

Question: PCI vs. CABG for cardiac outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute (95% CI)	
MACE											
1	observational studies	not serious	not serious	not serious	very serious [1,a]	none	13/25 (52.0%)	2/21 (9.5%)	**RR 10.29** (1.97 to 53.85)	**885 more per 1,000** (from 92 more to 1,000 more)	⨁◯◯◯ VERY LOW
Myocardial infarction											
1	observational studies	not serious	not serious	not serious	very serious [1,a]	none	3/25 (12.0%)	0/21 (0.0%)	**RR 6.69** (0.33 to 137.28)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW
Repeat revascularization/restenosis											
2	observational studies	not serious	not serious	not serious	serious [1,2,b]	none	25/44 (56.8%)	5/33 (15.2%)	**OR 7.38** (2.36 to 23.10)	**417 more per 1,000** (from 145 more to 653 more)	⨁◯◯◯ VERY LOW
Cardiac death											
1	observational studies	not serious	not serious	not serious	not serious [1]	none	1/25 (4.0%)	0/21 (0.0%)	**OR 2.63** (0.10 to 68.07)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW
Mean time between revascularization and MACE											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	CABG	Relative (95% CI)	Absolute (95% CI)	
1	observational studies	not serious	not serious	not serious	very serious [1,a]	none	25	21	-	MD **54.84 lower** (96.51 lower to 13.17 lower)	⨁◯◯◯ VERY LOW
Death from cardiovascular event											
1	observational studies	not serious	not serious	not serious	very serious [2,a]	none	2/19 (10.5%)	0/12 (0.0%)	**OR 3.57** (0.16 to 81.03)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW
Stroke											
1	observational studies	not serious	not serious	not serious	very serious [2,a]	none	1/19 (5.3%)	0/12 (0.0%)	**OR 2.03** (0.08 to 53.87)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Clinical action may differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision.
b. CI difference

References

1. Wang, X., Dang, A., Lv, N., Cheng, N., Cheng, X., Yang, Y., Song, Y.. Long-term outcomes of coronary artery bypass grafting versus percutaneous coronary intervention for Takayasu arteritis patients with coronary artery involvement. Seminars in Arthritis and Rheumatism; 2017.
2. Yang, Y., Tian, T., Yang, K., Zhang, Y., Meng, X., Fan, P., Feng, L., Mu, C., Gao, L., Zhou, X.. Outcomes of percutaneous coronary intervention and coronary artery bypass grafting in patients with Takayasu arteritis. International Journal of Cardiology; 2017.

Subgroup 2

Question: Surgical compared to Endovascular for Renal Artery Stenosis

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugical	Endovascular	Relative (95% CI)	Absolute (95% CI)	
Restenosis rate											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugical	Endovascular	Relative (95% CI)	Absolute (95% CI)	
1 [1]	observational studies	not serious	not serious	not serious	not serious	none	2/11 (18.2%)	6/19 (31.6%)	**OR 0.48** (0.08 to 2.95)	**134 fewer per 1,000** (from 280 fewer to 261 more)	⨁⨁◯◯ LOW
Rate of permeability at 5 years											
1 [1]	observational studies	not serious	not serious	not serious	not serious	none	9/11 (81.8%)	13/19 (68.4%)	**OR 2.08** (0.34 to 12.72)	**134 more per 1,000** (from 260 fewer to 281 more)	⨁⨁◯◯ LOW
Cure of hypertension											
1 [1]	observational studies	not serious	not serious	not serious	serious [a]	none	4/9 (44.4%)	3/14 (21.4%)	**OR 2.93** (0.47 to 18.33)	**230 more per 1,000** (from 101 fewer to 619 more)	⨁◯◯◯ VERY LOW
Chronic renal failure											
1 [1]	observational studies	not serious	not serious	not serious	not serious	none	0/9 (0.0%)	2/14 (14.3%)	**OR 0.26** (0.01 to 6.15)	**101 fewer per 1,000** (from 141 fewer to 363 more)	⨁⨁◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Clinical action may differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision.

References

1. Kinjo, H., Kafa, A.. The results of treatment in renal artery stenosis due to Takayasu disease: comparison between surgery, angioplasty, and stenting. A monocentrique retrospective study. G Chir; 2015

Subgroup 3

Question: Surgical Vascular compared to Endovascular in Various Arterial Lesions

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical Vascular	Endovascular	Relative (95% CI)	Absolute (95% CI)	
Early complications of procedures											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical Vascular	Endovascular	Relative (95% CI)	Absolute (95% CI)	
2 [1,2]	observational studies	not serious	not serious	not serious	not serious	none	19/117 (16.2%)	7/41 (17.1%)	**RR 0.96** (0.37 to 2.53)	**7 fewer per 1,000** (from 108 fewer to 261 more)	⨁⨁◯◯ LOW
Restensosis rate after 1 month											
3 [1,2,3]	observational studies	serious [1,2,3,a]	not serious	not serious	not serious	none	36/150 (24.0%)	32/72 (44.4%)	**OR 0.39** (0.21 to 0.72)	**207 fewer per 1,000** (from 301 fewer to 79 fewer)	⨁◯◯◯ VERY LOW
Late complications											
2 [1,2]	observational studies	not serious	not serious	not serious	not serious	none	37/117 (31.6%)	18/41 (43.9%)	**OR 0.55** (0.26 to 1.15)	**138 fewer per 1,000** (from 270 fewer to 35 more)	⨁⨁◯◯ LOW
Deaths associated with procedure											
1 [2]	observational studies	not serious	not serious	not serious	serious [2,b]	none	3/93 (3.2%)	1/26 (3.8%)	**OR 0.83** (0.08 to 8.36)	**6 fewer per 1,000** (from 35 fewer to 212 more)	⨁◯◯◯ VERY LOW
Any complication											
1 [2]	observational studies	not serious	not serious	not serious	not serious	none	34/93 (36.6%)	10/26 (38.5%)	**OR 0.92** (0.38 to 2.26)	**20 fewer per 1,000** (from 193 fewer to 201 more)	⨁⨁◯◯ LOW
Procedure failure when on immunosuppressives											
1 [3]	observational studies	serious [3,c]	not serious	not serious	not serious	none	1/15 (6.7%)	2/14 (14.3%)	**OR 0.43** (0.03 to 5.33)	**76 fewer per 1,000** (from 138 fewer to 328 more)	⨁◯◯◯ VERY LOW
Procedure failure when off immunosuppressives											
1 [3]	observational studies	serious [3,c]	not serious	not serious	not serious	none	6/18 (33.3%)	13/17 (76.5%)	**OR 0.15** (0.03 to 0.68)	**437 fewer per 1,000** (from 676 fewer to 76 fewer)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. In Y. Yang et. al. There is a higher percentage of cardiovascular risk factors in PCI group (e.g. HTN, DM, HLD) Also, in Y. W. Kim bypass group has more patients with active disease at the time of intervention.
b. Surgical consequences may differ if the upper versus the lower boundary of the CI represented the truth, leading to deaths associated with the procedure type thus was rated down to serious.
c. There are many differences between the groups in regards to the indication for the procedure; The population that underwent a surgery/procedure is mostly males which is not a good representation of the general population of Takayasu's arteritis (mostly females).

References

1. Kim, Y.,W., Kim, D.,I., Park, Y.,J., Yang, S.,S., Lee, G.,Y., Kim, D.,K., Kim, K., Sung, K.. Surgical bypass vs endovascular treatment for patients with supra-aortic arterial occlusive disease due to Takayasu arteritis. Journal of Vascular Surgery; 2012.
2. Labarca, C., Makol, A., Crowson, C.,S., Kermani, T.,A., Matteson, E.,L., Warrington, K.,J.. Retrospective Comparison of Open versus Endovascular Procedures for Takayasu Arteritis. Journal of Rheumatology; 2016.
3. Perera, A.,H., Youngstein, T., Gibbs, R.,G., Jackson, J.,E., Wolfe, J.,H., Mason, J.,C.. Optimizing the outcome of vascular intervention for Takayasu arteritis. Br J Surg; 2012.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

Author	Year	Title
Wang, X	2017	Long-term outcomes of coronary artery bypass grafting versus percutaneous coronary intervention for Takayasu arteritis patients with coronary artery involvement
Yang, Y	2017	Outcomes of percutaneous coronary intervention and coronary artery bypass grafting in patients with Takayasu arteritis
Kinjo, H	2015	The results of treatment in renal artery stenosis due to Takayasu disease: comparison between surgery, angioplasty, and stenting. A monocentrique retrospective study
Labarca, C	2016	Retrospective Comparison of Open versus Endovascular Procedures for Takayasu Arteritis
Perera, A	2014	Optimizing the outcome of vascular intervention for Takayasu arteritis
Kim, Y	2012	Surgical bypass vs endovascular treatment for patients with supra-aortic arterial occlusive disease due to Takayasu arteritis

Takayasu Arteritis (TAK)

Surgical Intervention

- **PICO question 25:** In patients with TAK/GCA undergoing surgical intervention, what is the impact of high dose prednisone use prior to procedure vs. not using high dose prednisone on disease-related outcomes and surgical intervention-related adverse effects?

- **Critical Outcomes:** Damage from disease, disease activity, relapse, infection, ischemic events, complications of the intervention such as bleeding or thrombotic events, need for additional intervention, death

127. In patients with TAK/GCA undergoing surgical intervention, what is the impact of high dose prednisone use prior to procedure vs. not using high dose prednisone on disease-related outcomes and surgical intervention-related adverse effects?

128. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high dose prednisone use prior to procedure	not using high dose prednisone	Relative (95% CI)	Absolute (95% CI)		
Symptoms relief												
1	observational studies	not serious	not serious	not serious	serious [a]	none	23/24 (95.8%)	11/22 (50.0%)	**RR 1.92** (1.25 to 2.93)	**460 more per 1,000** (from 125 more to 965 more)	⨁◯◯◯ VERY LOW	
Complications												
1	observational studies	not serious	not serious	not serious	serious [a]	strong association	1/24 (4.2%)	10/22 (45.5%)	**RR 0.09** (0.01 to 0.66)	**414 fewer per 1,000** (from 450 fewer to 155 fewer)	⨁⨁◯◯ LOW	
Death												
1	observational studies	not serious	not serious	not serious	very serious [a]	strong association	0/24 (0.0%)	1/22 (4.5%)	**RR 0.31** (0.01 to 7.16)	**31 fewer per 1,000** (from 45 fewer to 280 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Clinical action may differ if the upper versus the lower boundary of the CI represented the truth

2. In patients with TAK/GCA undergoing surgical intervention, what is the impact of high dose prednisone use prior to procedure on disease-related outcomes and surgical intervention-related adverse effects?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population	Results

					(Describe the intervention)	
Relief of symptoms were reported by 1 study with total 11 patients, follow-up 31.6 +- 27.4 months and rate of 100%	Chen, 2015	Case-series	Average follow-up 6-72 months	11 TAK patients undergoing surgery	Preoperative GC	11/11 (100%)
	Sharma, 2000	Case-series	Average follow-up 6-72 months	20 TAK patients undergoing balloon angioplasty	Preoperative GC	19/20 (95%)
Major complications were reported by 1 study with total 11 patients, follow-up 31.6 +- 27.4 months and rate of 18%	Chen, 2015	Case-series	Average follow-up 6-72 months	11 TAK patients undergoing surgery	Preoperative GC	2/11 (18%)
	Fields, 2006	Case-series	Average follow-up 6.7 years (range, 1 month to 19.3 years)	42 TAK patients undergoing surgery	GC 1mg/kg/day	11/42 (26%)
Failure of revascularization was reported by 1 study with total 11 patients, follow-up 31.6 +- 27.4 months and rate of 18%	Chen, 2015	Case-series	Average follow-up 6-72 months	11 TAK patients undergoing surgery	Preoperative GC	2/11 (18%)
Death	Chen, 2015	Case-series	Average follow-up 6-72 months	11 TAK patients undergoing surgery	Preoperative GC	1/11 (9%)
Freedom from revision at 5 and 10 years	Fields, 2006	Case-series	Average follow-up 6.7 years (range, 1 month to 19.3 years)	42 TAK patients undergoing surgery	GC 1mg/kg/day	100% in patients with quiescent disease not requiring steroids (group I, n=5), 95% and 81% in patients whose disease was quiescent on steroids (group II, n=24), 57% at

						both 5 and 10 years in patients with active disease on steroids (group III, n=7), and 33% at both 5 and 10 years in patients with active disease not on long-term steroids (group IV, n=6) (P<.006)
Restenosis	Sharma, 2000	Case-series	Average follow-up 6-72 months	20 TAK patients undergoing balloon angioplasty	Preoperative GC	2/20 (10%)

3. In patients with TAK/GCA undergoing surgical intervention, what is the impact of not using high dose prednisone on disease-related outcomes and surgical intervention-related adverse effects?

No single arm data available

References:

- Randomized controlled trials:
  None

- Comparative observational studies:

Author	Year	Title
Zheng	2018	Treatment with Corticosteroid and/or Immunosuppressive Agents before Surgery can Effectively Improve the Surgical Outcome in Patients with Takayasu's Arteritis

- Single arm studies:

Author	Year	Title
Chen	2015	Endovascular revascularization for carotid artery occlusion in patients with Takayasu arteritis
Fields	2006	Takayasu's arteritis: operative results and influence of disease activity
Sharma	2000	A follow-up study of balloon angioplasty and de-novo stenting in Takayasu arteritis

- Studies reviewed and excluded:

Author	Year	Title	Comments
W. Che	2018	Stenting for middle aortic syndrome caused by Takayasu arteritis-immediate and long-term outcomes	Exclude - low dose
K. Q. Yang	2017	Aortic Aneurysm in Takayasu Arteritis	exclude - low dose
M. Peng	2016	Selective stent placement versus balloon angioplasty for renovascular hypertension caused by Takayasu arteritis: Two-year results	exclude - low dose
A. Kalangos	2006	Long-term outcome after surgical intervention and interventional procedures for the management of Takayasu's arteritis in children	exclude - less than 10 pts
M. C. Park	2006	Post-interventional immunosuppressive treatment and vascular restenosis in Takayasu's arteritis	exclude - GC used after surgery
M. C. Park	2005	Clinical characteristics and outcomes of Takayasu's arteritis: analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification	exclude - mixed treatments, no clear distinction who got what
M. Ando	2000	Surgical considerations of occlusive lesions associated with Takayasu's arteritis	exclude - mixed data
M. Okita	2000	Evaluation of the results of surgical treatment for dilative lesions associated with Takayasu's arteritis	exclude - mixed data

Takayasu Arteritis (TAK)

Surgical Intervention

- **PICO question 26:** In patients with TAK with renovascular hypertension and renal artery stenosis, what is the impact of surgical intervention vs. treating with immunosuppression on hypertension, surgical intervention-related adverse events, and treatment-related adverse events?

- **Critical Outcomes:** Damage from disease (e.g., worsening of hypertension), infection, complications of the intervention such as bleeding or thrombotic events, need for additional intervention, serious adverse effects, toxicity, death

129. In patients with TAK with renovascular hypertension and renal artery stenosis, what is the impact of surgical intervention vs. treating with immunosuppression on hypertension, surgical intervention-related adverse events, and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugical	Endovascular	Relative (95% CI)	Absolute (95% CI)	
Restenosis rate											
1	observational studies	not serious	not serious	serious [a]	not serious	none	2/11 (18.2%)	6/19 (31.6%)	**OR 0.48** (0.08 to 2.95)	**134 fewer per 1,000** (from 280 fewer to 261 more)	⨁◯◯◯ VERY LOW
Rate of permeability at 5 years											
1	observational studies	not serious	not serious	serious [a]	not serious	none	9/11 (81.8%)	13/19 (68.4%)	**OR 2.08** (0.34 to 12.72)	**134 more per 1,000** (from 260 fewer to 281 more)	⨁◯◯◯ VERY LOW
Cure of hypertension											
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	4/9 (44.4%)	3/14 (21.4%)	**OR 2.93** (0.47 to 18.33)	**230 more per 1,000** (from 101 fewer to 619 more)	⨁◯◯◯ VERY LOW
Chronic renal failure											
1	observational studies	not serious	not serious	serious [a]	not serious	none	0/9 (0.0%)	2/14 (14.3%)	**OR 0.26** (0.01 to 6.15)	**101 fewer per 1,000** (from 141 fewer to 363 more)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. This study indirectly answers the PICO question by comparing surgical VS endovascular management for renal artery stenosis
b. Clinical action may differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision.

2. In patients with TAK with renovascular hypertension and renal artery stenosis, what is the impact of surgical intervention on hypertension, surgical intervention-related adverse events, and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results

Complications In 172 TAK patients, surgical intervention (stent, balloon, surgery) there were 21 complications (though ham study reported complications on entire cohort*). Overall reasonable safety of performing intervention in RAS	Ham, 2010	retrospective	75 months	55 patients, 31 with TAK (24 with fibromuscular dysplasia). Of the TAK patients, all had hypertension and 7 had renal insufficiency. There were 2 balloon angioplasties, 34 aortorenal bypass, 3 aortorenal bypass with ex vivo repair, 3 visceral-renal bypass, 5 nephrectomy	Open revascularization and renal artery PCTA with or without stenting. Patency of renal revascularization was assessed by serial duplex ultrasonography at 1 and 6 months after the intervention, then annually thereafter	8 major complications (10%) in 7 patients, including intra-abdominal bleeding requiring reexploration (n=3), wound infection (n=2), myocardial infarction (n=1), mesenteric ischemia requiring superior mesenteric revascularization (n=1), and retroperitoneal hematoma after PTA with stent (n=1). There were no postoperative deaths
	Weaver, 2004	retrospective	68 months	27 patients with TAK and renal artery stenosis with HTN underwent revascularization. All patients had rec'd steroids previously and 13 were on steroids at time of intervention. 8 had previously undergone renal interventions	32 aortorenal bypass procedures, 2 renal artery reimplantations, 4 nephrectomies and 2 transluminal angioplasty procedures	Morbidity was 19% with 2 wound infections, 1 MI, 1 retroperitoneal hematoma requiring repeat exploration and 1 mesenteric ischemia requiring SMA revascularization. No postoperative deaths
	Sharma, 1998	retrospective	22 months	96 stenosis in 66 TAK patients underwent PTRA (percutaneous transluminal renal angioplasty) for management of HTN 2/2 renal artery stenosis.	All TAK patients underwent PTRA. Indications included HTN uncontrolled with one drug, e/o >70% stenosis in the renal artery with peak systolic gradient of >20mmHg, AND clinically inactive disease	Complications included transient intrarenal arterial spasm in 3 patients, groin hematoma in 2 patients and ipsilateral renal vein injury in 1 patient

	Khalilullah, 1992	Retrospective	5-14 months	48 TAK patients undergoing renal artery stenosis angioplasty with 64 stenotic lesions	Renal angioplasty	One patient developed intimal flap. One small pseudoaneurysm of the brachial artery. No other complications
Blood Pressure— 333 cases of TAK treated with angioplasty or surgery for renal artery stenosis. BP showed significant improvement post procedure with cure or improvement in most patients. Decrease consistently in # of antihypertensive meds post intervention. Strongly favors intervention	Ham, 2010	retrospective	75 months	55 patients, 31 with TAK (24 with fibromuscular dysplasia). Of the TAK patients, all had hypertension and 7 had renal insufficiency. There were 2 balloon angioplasties, 34 aortorenal bypass, 3 aortorenal bypass with ex vivo repair, 3 visceral-renal bypass, 5 nephrectomy	Open revascularization and renal artery PCTA with or without stenting. Patency of renal revascularization was assessed by serial duplex ultrasonography at 1 and 6 months after the intervention, then annually thereafter	BP in TAK patients went from 171/102 pre intervention to 131/79 post intervention # of antihypertensive meds went from 2.4 to 1.0
	Hong, 2017	retrospective	118 months	TAK patients with renal artery involvement based on CT or angiography. Poor outcomes defined as refractory HTN, chronic renal insufficiency or death.	Of 62 TAK patients with RA involvement, 11 underwent RA revascularization	3/9 had refractory hypertension
	Tyagi, 1997	retrospective	4-108 months	35 children (age 5-14, mean 10.8) with severe HTN and RAS (>75% stenosed). 31 with TAK	Percutaneous transluminal renal angioplasty was performed after aortogram.	Of the 26 successful cases, 8 had cure in BP, 16 had improved BP and 2 had no response
	Weaver, 2004	retrospective	68 months	27 patients with TAK and renal artery stenosis with HTN underwent revascularization. All patients had rec'd steroids previously and 13 were on steroids at time	32 aortorenal bypass procedures, 2 renal artery reimplantations, 4 nephrectomies and 2 transluminal angioplasty procedures	BP improved from 167/99 to 132/79 Antihypertensive medication use went from 2.5 to 1 per patient. 10 patients had normal BP without any antihypertensive med, 2 with

				of intervention. 8 had previously undergone renal interventions		no improvement and 15 with improvement
	Lagneau, 1985	Retrospective	45 months	35 patients with TAK, 21 had significant hypertension and arteritis of the renal arteries. 18 patients required operation for severe unrelenting HTN resistant to medical therapy	18 TAK patients had surgical intervention (4 nephrectomy, 13 bypass graft procedures, 1 direct re-implantation)	12/18 were cured (BP <140/90) and 5 were improved.
	Dong 1987	Retrospective	25.5 months	32 patients with arteritis undergoing PCTA for renovascular HTN, but only 22 followed for 6 months post op	PCTA in 22 TAK patients for renovascular HTN	183/122 to 141/91 after follow up HTN cured in 18 of the 22
	Sharma, 1998	retrospective	22 months	96 stenosis in 66 TAK patients underwent PTRA (percutaneous transluminal renal angioplasty) for management of HTN 2/2 renal artery stenosis.	All TAK patients underwent PTRA. Indications included HTN uncontrolled with one drug, e/o >70% stenosis in the renal artery with peak systolic gradient of >20mmHg, AND clinically inactive disease	Systolic BP decreased from 95mmHg to 9mmHg. BP improved from 181/115 to 136/86. Antihypertensive drug requirement decreased from 3.9 to 1.1.
	Dong, 2002	retrospective	92.5 months	87 cases of renovascular stenosis treated wth PTRA of which 49 had arteritis.	49 TAK patients Underwent PRTA	BP went from 196/127 to 144/91 post intervention. Cured in 33 (50.8%), improved in 20 (30.8%), poor outcome in 12 (18.4%)
Primary Patency	Ham, 2010	retrospective	75 months	55 patients, 31 with TAK (24 with fibromuscular dysplasia). Of the TAK patients, all had	Open revascularization and renal artery PCTA with or without stenting.	primary patency rate was 75% in TAK at 5 years

203 TAK patients with revascularization of renal artery with high primary patency rates at 1 year.				hypertension and 7 had renal insufficiency. There were 2 balloon angioplasties, 34 aortorenal bypass, 3 aortorenal bypass with ex vivo repair, 3 visceral-renal bypass, 5 nephrectomy	Patency of renal revascularization was assessed by serial duplex ultrasonography at 1 and 6 months after the intervention, then annually thereafter	
	Tyagi, 1997	retrospective	4-108 months	35 children (age 5-14, mean 10.8) with severe HTN and RAS (>75%stenosed). 31 with TAK	Percutaneous transluminal renal angioplasty was performed after aortogram.	Unsuccessful in 5/31, Successful procedure in 26 TAK cases
	Weaver, 2004	retrospective	68 months	27 patients with TAK and renal artery stenosis with HTN underwent revascularization. All patients had rec'd steroids previously and 13 were on steroids at time of intervention. 8 had previously undergone renal interventions	32 aortorenal bypass procedures, 2 renal artery reimplantations, 4 nephrectomies and 2 transluminal angioplasty procedures	Primary patency of the renal revascularization at 1, 3, and 5 years was 87%, 79%, and 79%, respectively
	Sharma, 1998	retrospective	22 months	96 stenosis in 66 TAK patients underwent PTRA (percutaneous transluminal renal angioplasty) for management of HTN 2/2 renal artery stenosis.	All TAK patients underwent PTRA. Indications included HTN uncontrolled with one drug, e/o >70% stenosis in the renal artery with peak systolic gradient of >20mmHg, AND clinically inactive disease	Successful intervention in 91 (95%) of stenosis in 62/66 patients. Clinical success in 59 (89%). Stenosis decreased from 88% to 11%
	Khalilullah, 1992	Retrospective	5-14 months	48 TAK patients undergoing renal artery	Renal angioplasty	58/64 (90.6%) of stenotic lesions could be successfully dilated.

				stenosis angioplasty with 64 stenotic lesions		
Death 5 deaths in 138 TAK patients undergiongint erventionàlow mortality	Ham, 2010	retrospective	75 months	55 patients, 31 with TAK (24 with fibromuscular dysplasia). Of the TAK patients, all had hypertension and 7 had renal insufficiency. There were 2 balloon angioplasties, 34 aortorenal bypass, 3 aortorenal bypass with ex vivo repair, 3 visceral-renal bypass, 5 nephrectomy	Open revascularization and renal artery PCTA with or without stenting. Patency of renal revascularization was assessed by serial duplex ultrasonography at 1 and 6 months after the intervention, then annually thereafter	0/31 died
	Hong, 2017	retrospective	118 months	TAK patients with renal artery involvement based on CT or angiography. Poor outcomes defined as refractory HTN, chronic renal insufficiency or death.	Of 62 TAK patients with RA involvement, 11 underwent RA revascularization	1/9 died
	Weaver, 2004	retrospective	68 months	27 patients with TAK and renal artery stenosis with HTN underwent revascularization. All patients had rec'd steroids previously and 13 were on steroids at time of intervention. 8 had previously undergone renal interventions	32 aortorenal bypass procedures, 2 renal artery reimplantations, 4 nephrectomies and 2 transluminal angioplasty procedures	3 deaths (9 months, 9 years and 14 years) none post-op
	Lagneau, 1985	Retrospective	45 months	35 patients with TAK, 21 had significant hypertension and arteritis of the renal arteries. 18	18 TAK patients had surgical intervention (4 nephrectomy, 13 bypass	No failures, 1 died of sepsis post op

				patients required operation for severe unrelenting HTN resistant to medical therapy	graft procedures, 1 direct re-implantation)	
Renal function- 27 patients with overall improvmeent in GFR and renal function. 2/3 came off of dialysis	Weaver, 2004	retrospective	68 months	27 patients with TAK and renal artery stenosis with HTN underwent revascularization. All patients had rec'd steroids previously and 13 were on steroids at time of intervention. 8 had previously undergone renal interventions	32 aortorenal bypass procedures, 2 renal artery reimplantations, 4 nephrectomies and 2 transluminal angioplasty procedures	3 on HD. Baseline creat was 1.2 in remaining 24 patients with GFR of 76. Post intervention Screat dec to 1 in the 24 patients on dialysis and GFR inc to 88. 2/3 HD patients got off of dialysis
Restenosis-93 TAK patients. 15 with restenosis or occlusion	Weaver, 2004	retrospective	68 months	27 patients with TAK and renal artery stenosis with HTN underwent revascularization. All patients had rec'd steroids previously and 13 were on steroids at time of intervention. 8 had previously undergone renal interventions	32 aortorenal bypass procedures, 2 renal artery reimplantations, 4 nephrectomies and 2 transluminal angioplasty procedures	3 graft stenosis (8%) and 3 graft occlusions (in 5 patients)
	Sharma, 1998	retrospective	22 months	96 stenosis in 66 TAK patients underwent PTRA (percutaneous transluminal renal angioplasty) for management of HTN 2/2 renal artery stenosis.	All TAK patients underwent PTRA. Indications included HTN uncontrolled with one drug, e/o >70% stenosis in the renal artery with peak systolic gradient of >20mmHg, AND clinically inactive disease	Restenosis rate (recurrence of htn and angiographic demonstration of restenosis) was 16% at 22 months

References:

- Randomized controlled trials:
  None

- Comparative observational studies:

Author	Year	Title
Kinjo, H	2015	The results of treatment in renal artery stenosis due to Takayasu disease: comparison between surgery, angioplasty, and stenting. A monocentrique retrospective study

- Single arm studies:

Author	Year	Title
Ham	2010	Late outcomes of endovascular and open revascularization for nonatherosclerotic renal artery disease
Weaver	2014	Renal revascularization in Takayasu arteritis-induced renal artery stenosis
Sharma	1998	Results of renal angioplasty in nonspecific aortoarteritis (Takayasu disease)
Khalilullah	1992	Percutaneous transluminal angioplasty in Takayasu arteritis
Hong	2017	Longterm Outcomes of Renal Artery Involvement in Takayasu Arteritis
Tyagi	1997	Percutaneous transluminal angioplasty for renovascular hypertension in children: initial and long-term results
Lagneau	1985	Renovascular hypertension and Takayasu's disease
Dong	1987	Percutaneous transluminal angioplasty for renovascular hypertension in arteritis: experience in China

Takayasu Arteritis (TAK)

Other

- **PICO question 27:** In patients with known TAK and known cervicocranial stenotic lesions, what is the impact of maintaining blood pressure <130/80 (or ≤ 95 percentile in children <13 years old based on NIH/CDC values) vs. permitting blood pressure to remain above these levels on disease-related outcomes and treatment-related adverse events?

- **Critical outcomes:** Organ damage from disease (e.g., Stroke, ischemia), serious adverse events, toxicity leading to drug discontinuation (e.g., Hypotension, bradycardia, elevated creatinine), death

131. In patients with known TAK and known cervicocranial stenotic lesions, what is the impact of maintaining blood pressure <130/80 (or ≤ 95 percentile in children <13 years old based on NIH/CDC values) vs. permitting blood pressure to remain above these levels on disease-related outcomes and treatment-related adverse events?
    - No data available

132. In patients with known TAK and known cervicocranial stenotic lesions, what is the impact of maintaining blood pressure <130/80 (or ≤ 95 percentile in children <13 years old based on NIH/CDC values) on disease-related outcomes and treatment-related adverse events?
    - No data available

133. In patients with known TAK and known cervicocranial stenotic lesions, what is the impact of permitting blood pressure to remain above these levels on disease-related outcomes and treatment-related adverse events?
    - No data available

References:

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

- Comments:

Author	**Year**	**Title**	**Comments**
W. Che	2018	Stenting for middle aortic syndrome caused by Takayasu arteritis-immediate and long-term outcomes	Surgical procedures, no BP control therapy. Exclude
T. A. Ladapo	2015	Impact of revascularization on hypertension in children with Takayasu's arteritis-induced renal artery stenosis: a 21-year review	Surgical procedures, no BP control therapy. Exclude
G. Zhu	2014	Angioplasty for pediatric renovascular hypertension: a 13-year experience	Surgical procedures, no BP control therapy. Exclude

T. Taketani	2005	Surgical treatment of atypical aortic coarctation complicating Takayasu's arteritis--experience with 33 cases over 44 years	Surgical procedures, no BP control therapy. Exclude
P. G. Beale	1992	Management of renal hypertension in children with Takayasu's arteritis using renal autografting or allograft transplantation in selected circumstances and total lymphoid irradiation	Surgical procedures, no BP control therapy. Exclude
J. M. Giordano	1991	Experience with surgical treatment of Takayasu's disease	Surgical procedures, no BP control therapy. Exclude
P. Lagneau	1987	Surgical treatment of Takayasu's disease	Surgical procedures, no BP control therapy. Exclude