TNF-α antagonists improve arterial stiffness in patients with rheumatoid arthritis: a meta-analysis

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Disclosures

No conflict of interest

- Background
- Methods
- Results
- Conclusions

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Background

EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis

M J L Peters,[1] D P M Symmons,[2] D McCarey,[3] B A C Dijkmans,[1,4] P Nicola,[5] T K Kvien,[6] I B McInnes,[7] H Haentzschel,[8] M A Gonzalez-Gay,[9] S Provan,[6] A Semb,[6] P Sidiropoulos,[10] G Kitas,[11] Y M Smulders,[12] M Soubrier,[13] Z Szekanecz,[14] N Sattar,[15] M T Nurmohamed[1,4,13]

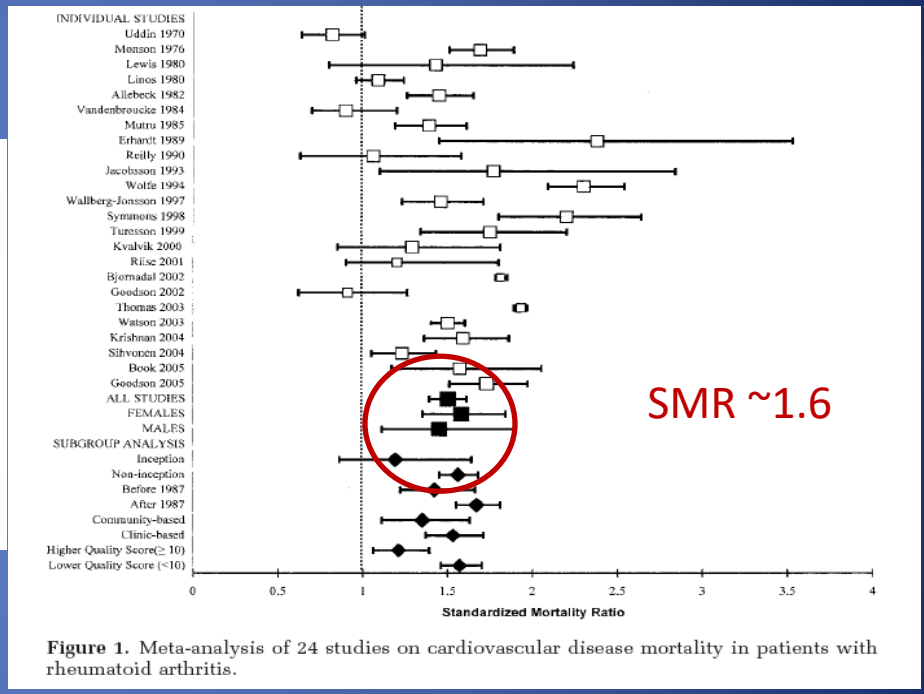
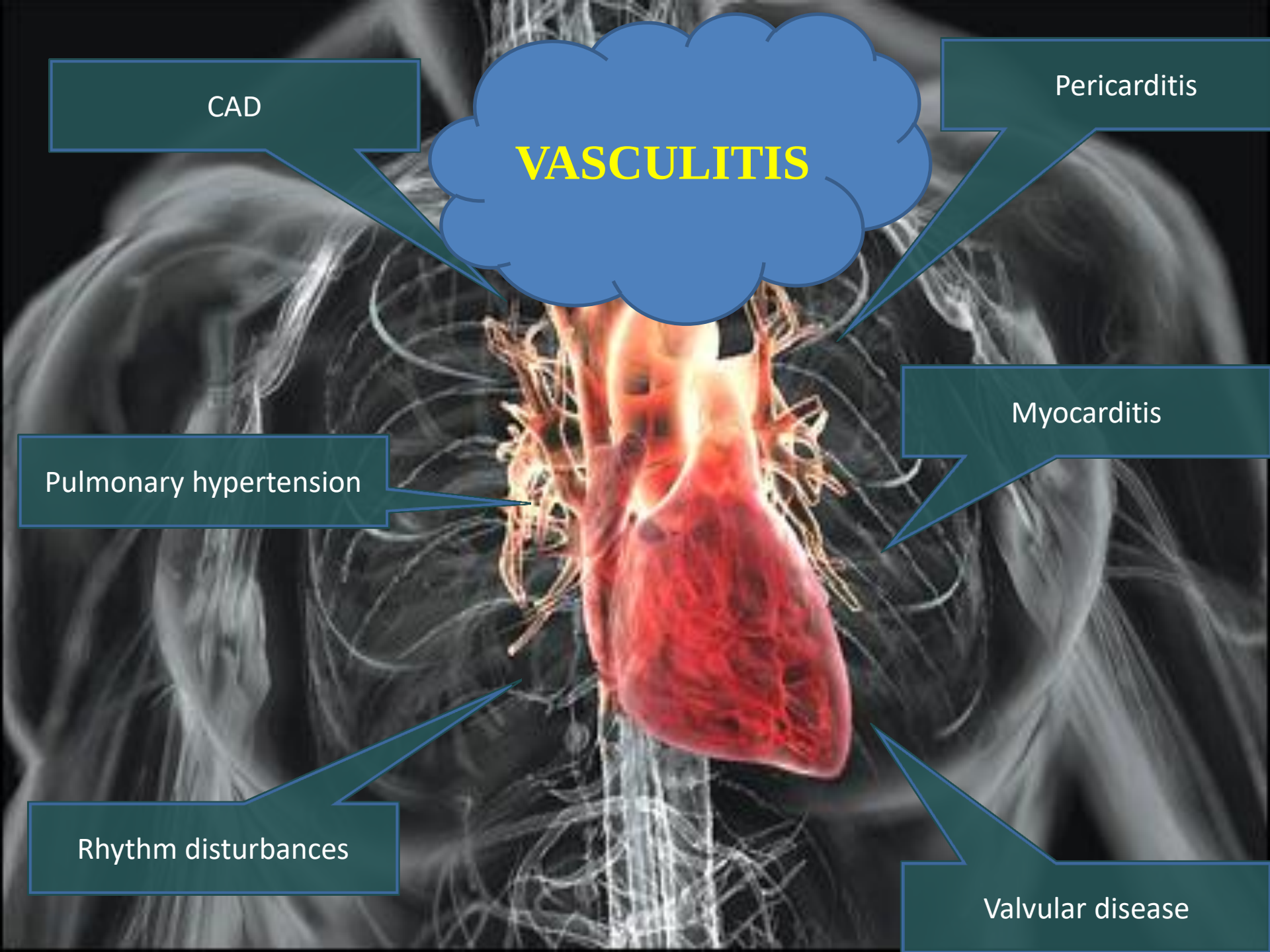


Figure 1. Meta-analysis of 24 studies on cardiovascular disease mortality in patients with rheumatoid arthritis.

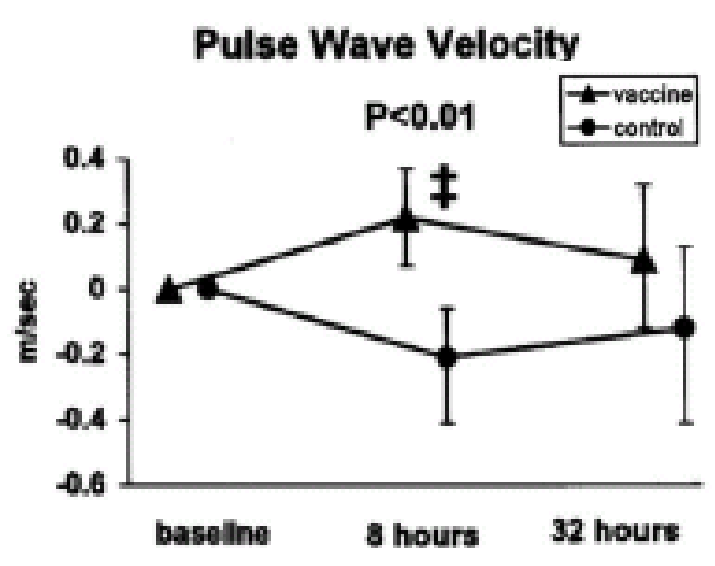
SMR ~1.6

Avina-Zubieta et al, Arthritis Rheum 2008

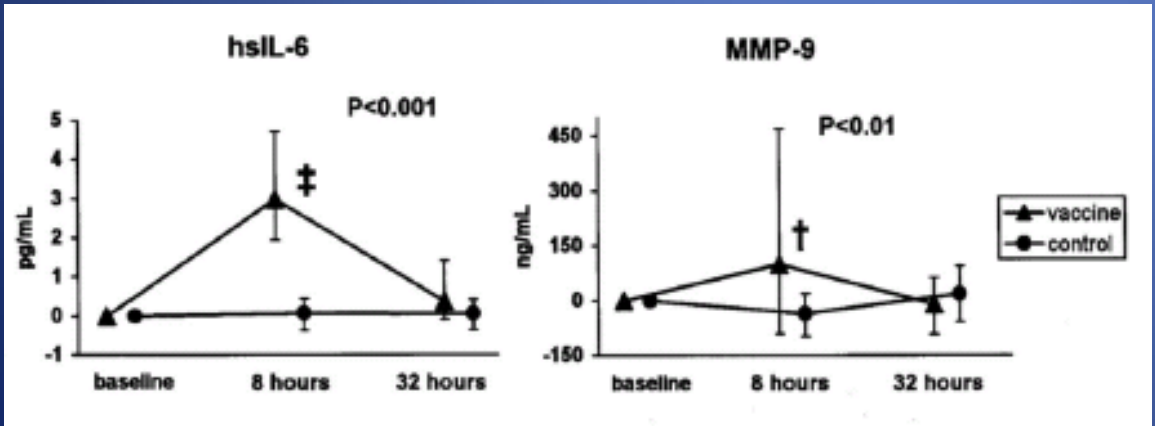
- RA is associated with increased mortality and morbidity, predominantly because of cardiovascular disease

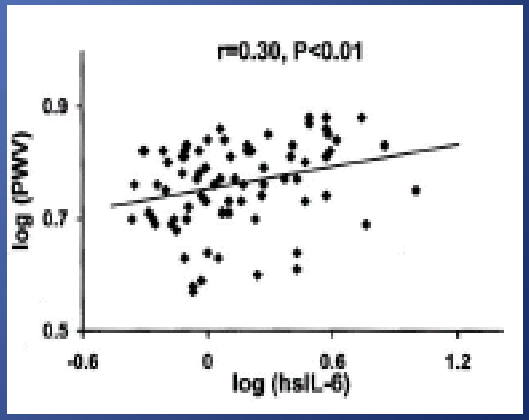

VASCULITIS
CAD
Pericarditis
Myocarditis
Pulmonary hypertension
Rhythm disturbances
Valvular disease

Acute inflammation and arterial function



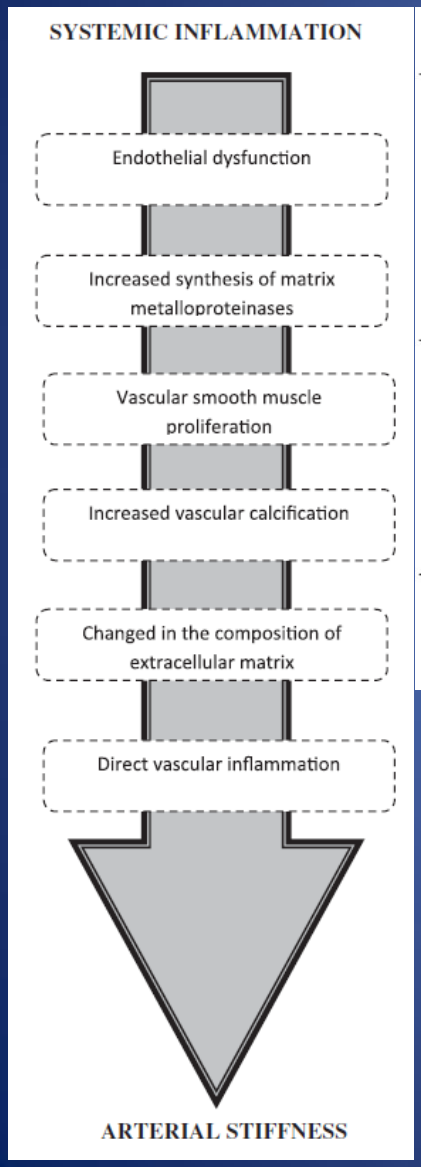
Acute inflammation-induced vascular impairment is associated with an increase of level of inflammatory mediators

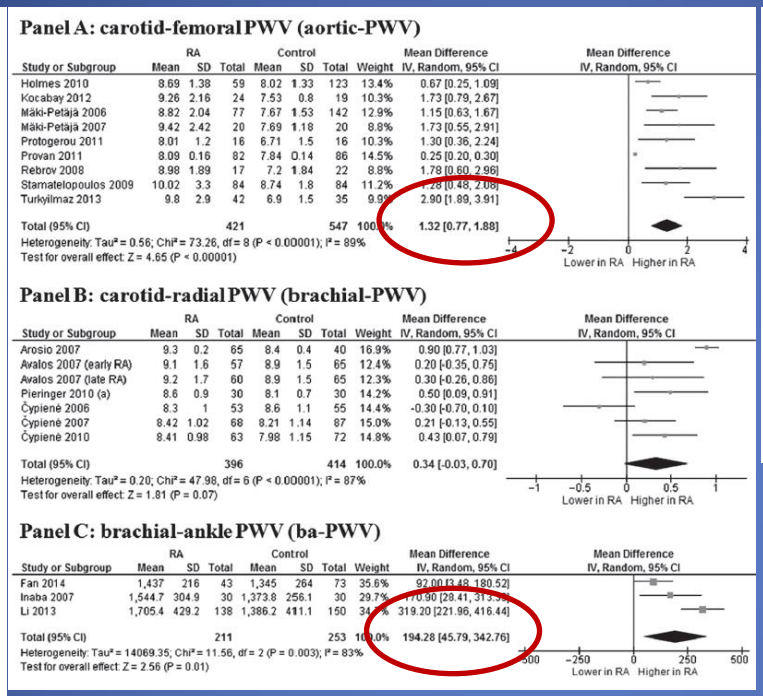


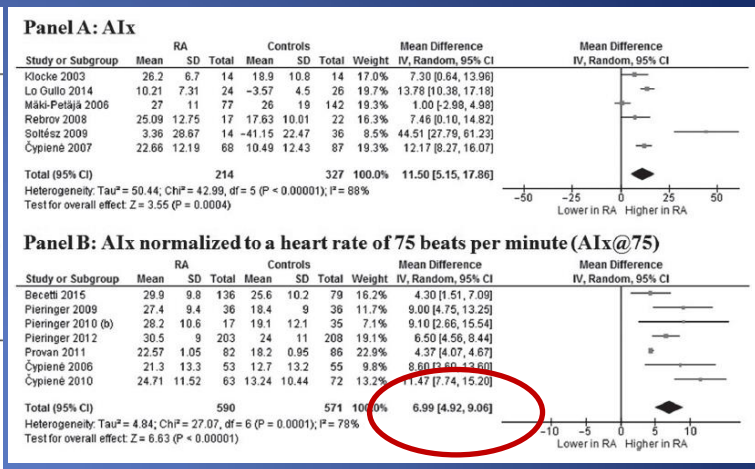


Vlachopoulos C, et al. Circulation 2005

Inflammation and arterial function



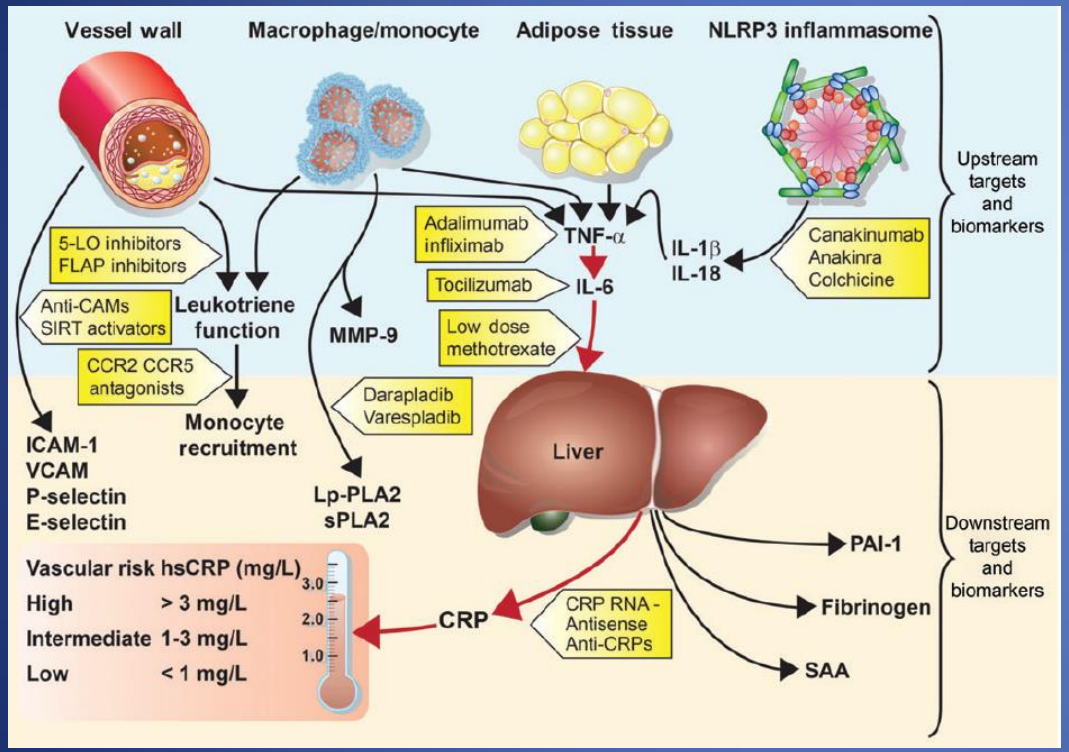




A strong body of evidence demonstrates that inflammation plays an important role in arterial stiffening

Mäki-Petäjä K and Wilkinson I Art Res 2012
Aznaouridis K and Stefanadis C Art Res 2007
Ambrosino et al., Ann Med 2015
Jain et al., Atherosclerois 2014

Anti-inflammatory treatments and cardiovascular disease



Clinical trials of anti-inflammatory therapy in cardiovascular disease

Drug	Target	Trial	Size	Sponsor	Status
A. Agents impacting on the IL-6 signalling pathway					
Canakinumab	IL-1β	CANTOS	10000	Novartis	Enrolling
Methotrexate	IL-6,TNF	CIRT	7000	NHLBI	Enrolling
Anakinra	IL-1Ra	IL-HEART	190	UK-MRC	Completed
Colchicine	multiple	LoDoCo	532	HRS, Aus	Positive
Tocilizumab	IL-6	Entracte	3000	Hoffmann	Enrolling
Etanercept	TNF	Entracte	3000	Hoffmann	Enrolling
B. Agents impacting on alternative inflammatory pathways					
Succinobucol	Ox-LDL	ARISE	6144	AtheroGenics	Negative
Varespladib	$sPLA_2$	VISTA-16	5000	Anthera	Negative
Darapladib	Lp-PLA_2	STABILITY	15000	GSK	Enrolled
Darapladib	Lp-PLA_2	SOLID-TIMI-52	13000	GSK	Enrolled
Inclacumab	P-Selectin	SELECT-ACS	544	Roche	Completed
Inclacumab	P-Selectin	SELECT-CABG	380	Roche	Enrolled

Inflammatory pathways as potential targets for atherosclerotic therapies

Ridker P and Lüscher T, EHJ 2014

Drug treatment of RA

- DMARDS (Methotrexate-Leflunomide)
- Biological therapies

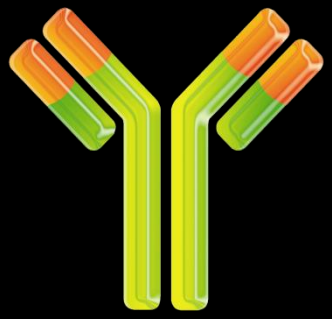
- Anti- TNFa	Infliximab
	Etanercept
	Adalimumab
	Golimumab
	Certolizumab pegol
- Anti- IL1	Anakinra
- Anti-IL6	Tocilizumab
- Anti-B cell	Rituximab
- Anti-T cell	Abatacept

± Corticosteroids

Types of biological agents

Monoclonal antibodies

Chimera



Anti-TNF-a
- Infliximab *(Remicade)*

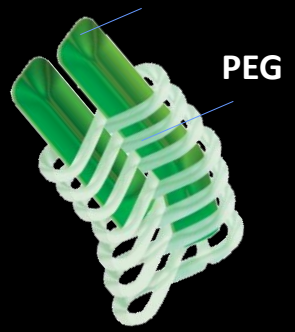
Anti-CD20
- Rituximab *(Mabthera)*

Human

Anti-TNF-a
- Adalimumab *(Humira)*
- Golimumab *(Simponi)*

Anti-IL6R
- Tocilizumab *(RoActemra)*

Pegylated



Anti-TNF-a
- Certolizumab pegol *(Cimzia)*

Recombinant proteins

Fusion protein

TNF-R
- Etanercept *(Enbrel)*

CTLA-4
- Abatacept *(Orencia)*

Recombinant protein

IL-1ra
- Kineret *(Anakinra)*

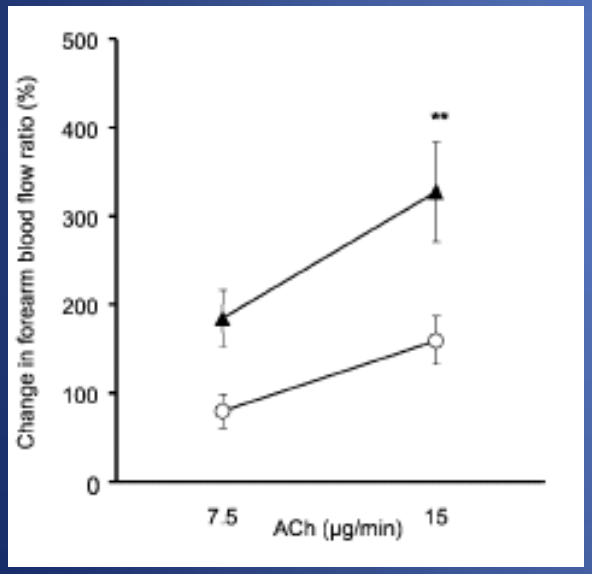
Anti-inflammatory drugs and arterial function

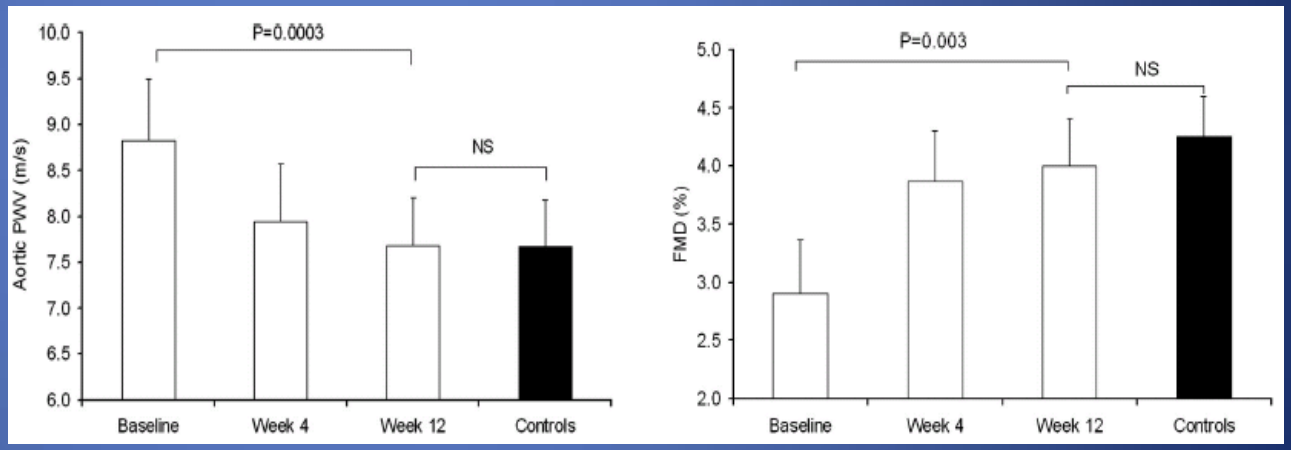
Chronic inflammatory diseases

anti-TNF factors

Systemic vasculitis

Rheumatoid arthritis





Maki-Petaja K, Hall F, Booth A et al, Circulation 2006

Boooth A, Jayne D, Kharbanda R, et al, Circulation 2004

TNF-a antagonists may have a beneficial effect on preventing the progression of subclinical atherosclerosis and arterial stiffness

Tam et al., Rheumatology 2014

Purposes of the meta-analysis

- To investigate the effect of TNF-a antagonists on arterial stiffness in RA patients
- To investigate whether publication bias could have affected our results
- To evaluate the effect of different moderators on the association of TNF-a antagonists and arterial stiffness

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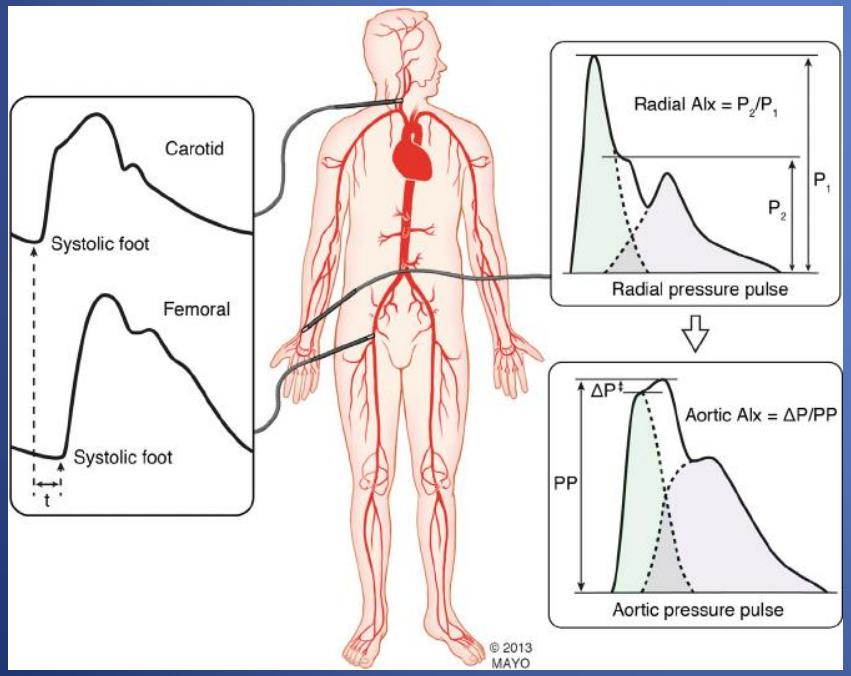
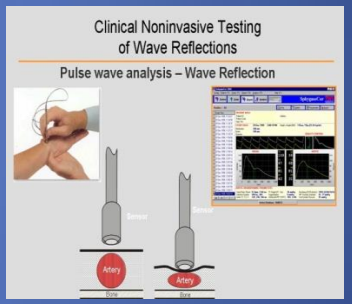
Outcomes of meta-analysis

The pooled mean difference separately for

1) Carotid-femoral pulse wave velocity (PWV) and
2) Aortic augmentation index (AIx)





Study eligibility

1) full-length publications in peer-reviewed journals or abstracts in international cardiovascular congresses
2) administration of anti-TNF antagonists for a minimum duration of 6 weeks
3) measurements of arterial stiffness and augmentation index in compliance to standard criteria
4) baseline and follow-up values
5) anti-TNF antagonists were administered in patients (n > 8) with overlapping rheumatic diseases (including among others rheumatoid arthritis and sero -negative arthritis)
6) studies including only patients with psoriatic arthritis, ankylosing spondylitis or other diseases or patients receiving other biologic agents were excluded from this meta-analysis

Literature search

- We performed a systematic review of the English and non-English literature in the PubMed, Cochrane and Embase databases until 08/2016 questing for studies that implemented anti-TNF antagonists in patients with rheumatic diseases and reported indices of arterial stiffness and central haemodynamics before and after initiation of treatment.
- The search terms were “TNF- antagonists” OR “anti- TNFs” AND “augmentation index”, OR “pulse wave velocity”, OR “arterial stiffness”, AND “rheumatoid arthritis”. The references and related articles of eligible articles were also scanned for additional studies that could be incorporated in our meta-analysis. Abstracts from international cardiovascular congresses were also retrieved when applicable.

Data, statistical and quality analysis (1)

- The algebraic difference in PWV and/or AIx between the follow-up and the baseline visit was reported for each study along with measures of variance (i.e. standard error of the difference).
- These differences were provided unadjusted and summarize the direction and magnitude of arterial stiffness change following anti-TNF treatment
- Fixed-effects models were implemented
- To test whether the true effect in all studies is the same (i.e. heterogeneity), we used the I-squared measure I^2 that permits quantification of discrepancy among studies
- We conducted a between-study subgroup analysis to evaluate whether the estimates of the effect of anti-TNFs on vascular indices differ within certain populations (prevalence of male gender below or over 40% within the study sample, age, responders versus non responders to therapy). Differences in changes of vascular indices between subgroups were compared with a test of interaction

Data, statistical and quality analysis (2)

- The presence of publication bias was investigated graphically by funnel plots of precision and the Duval and Tweedie trim-and-fill method.
- We evaluated the quality of the included studies by assessing selection bias, detection bias, and attrition bias.
- All analyses were performed with STATA package, version 11.1 (StataCorp, College Station, Texas USA)

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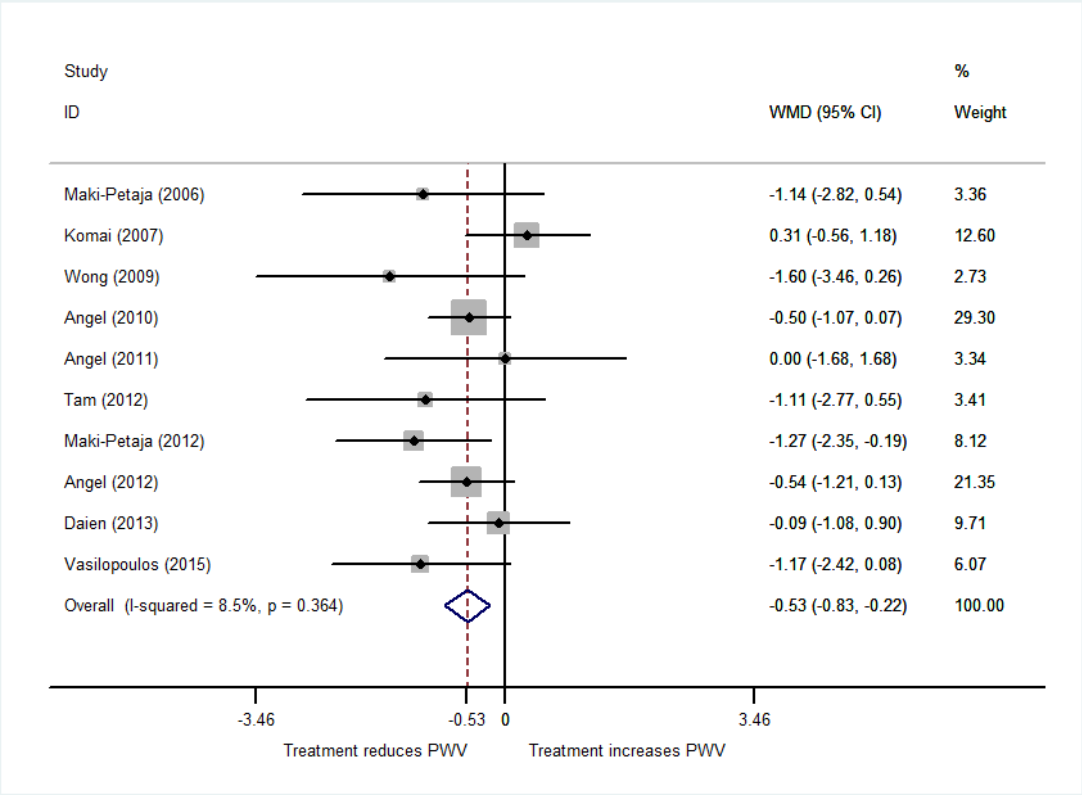
Results
Selection flowchart and Qualitive summary

- The meta-analysis included 14 studies with 320 patients. Studies that were incorporated in the meta-analysis were published since 2005
- Corresponding sample sizes ranged from 9 to 64 individuals and the median follow-up period ranged from 6 to 56 weeks.
- The median age was 54 years (inter-quartile range: 48-57) and 27% of the total population under study were male.
- The median duration of rheumatic disease previous to anti-TNF therapy was 10 years (inter-quartile range: 8.5-12.5).
- 72% (inter-quartile range: 51-100%) of the patients were under treatment with one or more DMARD(s) before initiation of anti-TNF therapy.
- Baseline ESR was 37mm/hr (inter-quartile range: 16-40) and baseline DAS28 (Disease Activity Score Calculator for Rheumatoid Arthritis) was 5.52 (inter-quartile range: 4.8- 6.52).
- Infliximab was used in 9, etanercept in 8 and adalimumab in 6 studies.

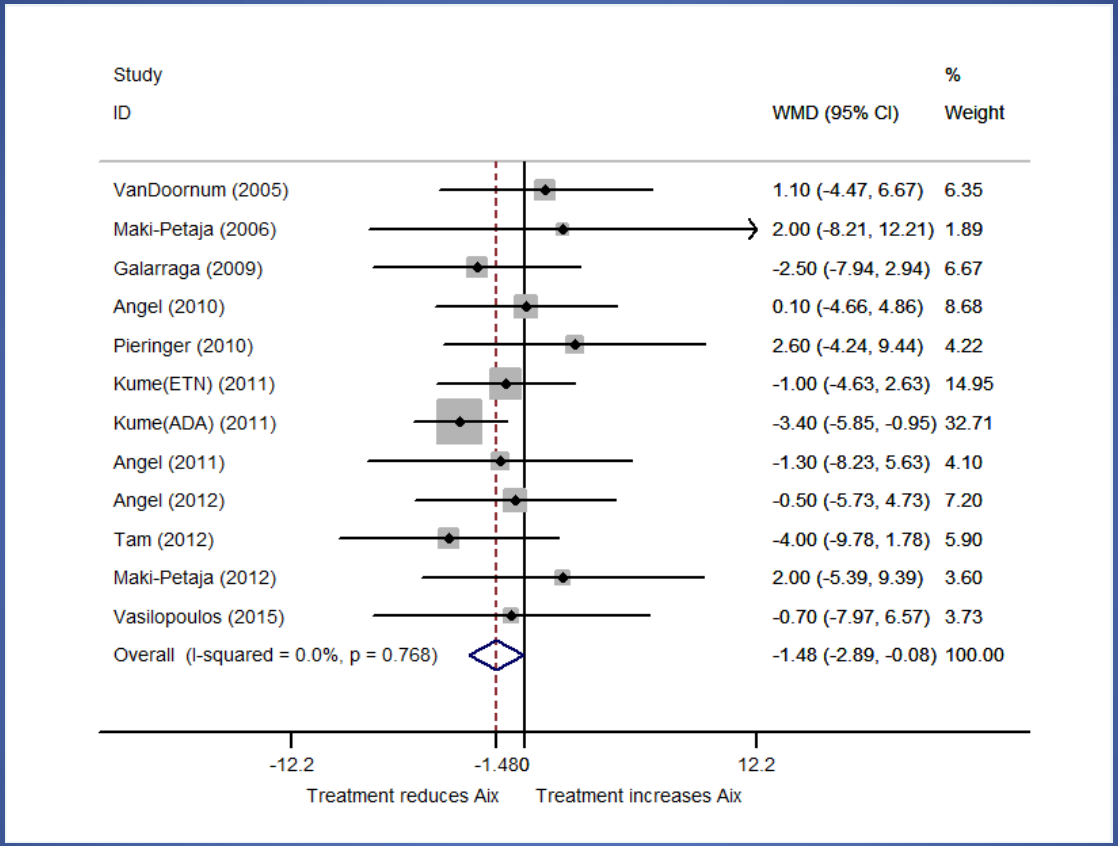
Study	Study design	Outcome measures	Results	Comments/ Limitations
Van Doornum et al. (2005) (9)	Either Etanercept/Adalimumab/ Infliximab for 6 wk in 14 RA patients	1.Augmentation index (AIx)	1. AIx did not change during the study period (P =0.504)	Small sample size, only AIx used
Mäki-Petäjä et al. (2006) (8)	Administration of etanercept for 12 wk in 9 RA patients compared to a nontreatment control group	1. Aortic PWV 2. Augmentation index(AIx) 3. Brachial PWV	1. Aortic PWV reduced significantly at weeks 4 and 12 and comparable to control subjects at 12 wks (P =0.0003) 2. Augmentation index did not change significantly over the study period (P =0.6) 3. Brachial PWV did not change significantly over the study period (P = 0.8)	Small size, not prospective study, nonrandomized design of the study
Cypiene et al. (2007) (10)	Retrospective study in 15 RA patients taking infliximab compared to nontreatment group	1. Brachial PWV 2.Augmentation index(AIx)	1. Brachial PWV reduced significantly compared to controls (P = 0.004) 2. Augmentation index unchanged when compared to controls (P=NS)	Retrospective study, no placebo-controlled group, no blinding and randomization
Komai et al. (2007) (11)	Administration of infliximab for 6 wks in 15 Japanese RA patients	1. Aortic PWV	1. Aortic PWV remain unchanged at weeks 2 and 6 of the study period (P=NS)	Small size, possible ethnic differences
Wong et al. (2009) (12)	Administration of infliximab for 56 wk in 26 RA patients	1. Aortic PWV 2.Augmentation index(AIx)	1. Aortic PWV reduced significantly over the 56 wk (P =0.004) 2. Augmentation index unchanged (P =0.265)	Small size, lack of vascular outcome measures before 24 weeks
Galarraga et al. (2009) (13)	Etanercept administered to 26 RA patients for 4 mo compared to control group of 21 RA patients taking methotrexate	1. Augmentation index corrected for 75 bpm (AIx@75)	1. AIx@75 significantly improved at 2 and 4 mo (in etanercept group)(P =0.025) but not in methotrexate group (P = 0.971)	Only AIx used, significant differences between the groups were observed at baseline
Angel et al. (2010) (14)	Either etanercept/ adalimumab/infliximab administered for 3 mo in 60 arthritic patients compared to a nontreatment control group	1. Aortic PWV 2.Augmentation index(AIx)	1. Aortic PWV reduced significantly after 3 mo in all patients including RA patients compared to controls (P =0.002 and 0.05, respectively) 2. Augmentation index did not change significantly in all patients (P =0.53)	The exclusion/inclusion criteria were vague / not implemented fully
Pieringer et al. (2010) (15)	Infliximab administered to 30 Patients (17 RA, 13 AS) for 6 wks compared to a nontreatment control group	1. Augmentation index corrected for 75 bpm (AIx@75)	1. AIx@75 significantly increased over the study period in all patients (and RA subgroup) (P =0.03 and P = 0.01 respectively)	Small number of patients, short follow up period, differences between RA and AS patients
Angel et al (2011) (16)	17 patients with RA, AS, or PsA who had been treated with infliximab for at least 12 months.	1. Aortic PWV 2.Augmentation index(AIx)	1. Aortic PWV remain unchanged (P=NS) 2. Augmentation index did not change significantly (P=NS)	Small size,three types of inflammatory arthropathies
Kume et al. (2011) (17)	Patients were randomly assigned to receive TCZ alone (n = 22), ETN alone (n = 21), or ADA alone (n = 21) for 24 weeks	1. CAVI 2. AIx	1. CAVI was significantly reduced in all groups 2. AIx was significantly reduced in all groups	Small sample size, only AIx used
Angel et al (2012) (18)	Fifty-five patients with RA, AS, or PsA. Thirty-six patients starting with anti-TNF-α therapy were compared with a nontreatment group of 19 patients.	1. Aortic PWV 2. cIMT	1.After 1 year, PWV was improved in the treatment group (P=0.04), but not in the control group 2.CIMT progression was reduced in the treatment group (P=0.01) compared to the control group	Small size, nonrandomized design
Mäki-Petäjä et al. (2012) (19)	17 patients with RA, before and after 8 weeks of anti-tumor necrosis factor-α therapy by using (18)F-fluorodeoxyglucose positron emission tomography compared to control group (n=34)	1. (TBRs) 2. PWV	1. TBR was significantly decreased 2. PWV was significantly decreased	Small sample size, only PWV used
Tam et al (2012) (20)	A randomized, open-label study in which early RA patients with active disease were treated with MTX alone (n = 20) and MTX plus infliximab (n = 20) for 6 months	1. Aortic PWV 2.Augmentation index(AIx) 3.Intima-media thickness (IMT)	1. At 6 months, there was a significantly greater reduction in PWV in the MTX plus IFX group (P = 0.044) 2,3. The changes in IMT and AIx were similar between the 2 groups.	Absence of a direct control group
Daien et al (2013) (21)	Etanercept administered in 28 RA pts for 6 months compared to 20 pts receiving sDMARDs	1. LVMI 2. PWV	1. LVMI was significantly decreased in ETN group but not in control group 2. PWV was not decreased in either group	Small sample size, only PWV used
Vassilopoulos et al (2015) (22)	Adalimumab (ADA) administered in 18 RA patients for 12 wks compared to 18 RA patients receiving ADA±MTX for 3 months	1. Augmentation index corrected for 75 bpm (AIx@75) 2. Aortic PWV	1. Augmentation index did not change significantly over the study period in all patients (P=0.67) 2. Aortic PWV reduced significantly in ADA group but not in MTX group (P=0.02 and P=0.90, respectively)	Small number of patients, short period of treatment and absence of a direct control group

Results



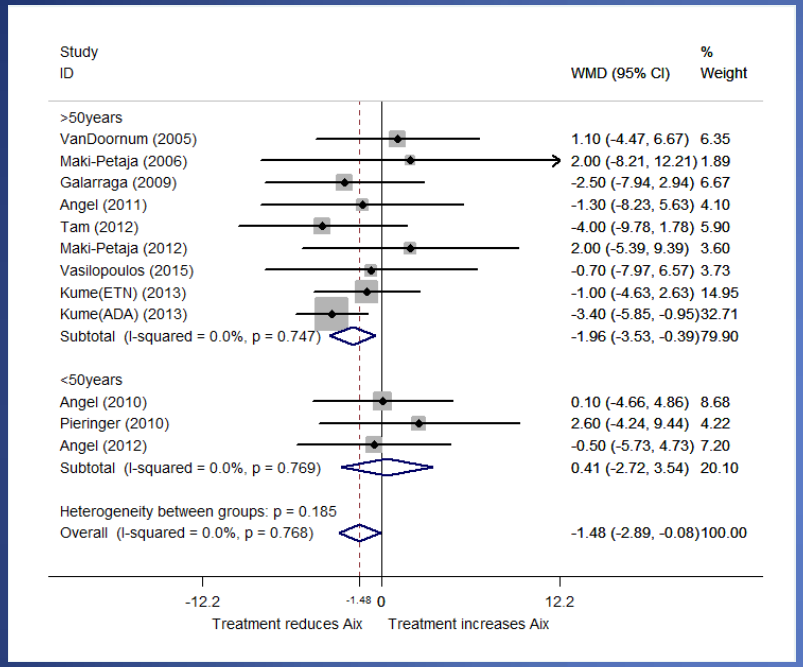
- Subjects under therapy with anti-TNFs significantly decreased their arterial stiffness (mean change in PWV: -0.53 m/s, p=0.001)
- No significant heterogeneity was observed across the studies (I^2=8.5% , p=0.364)

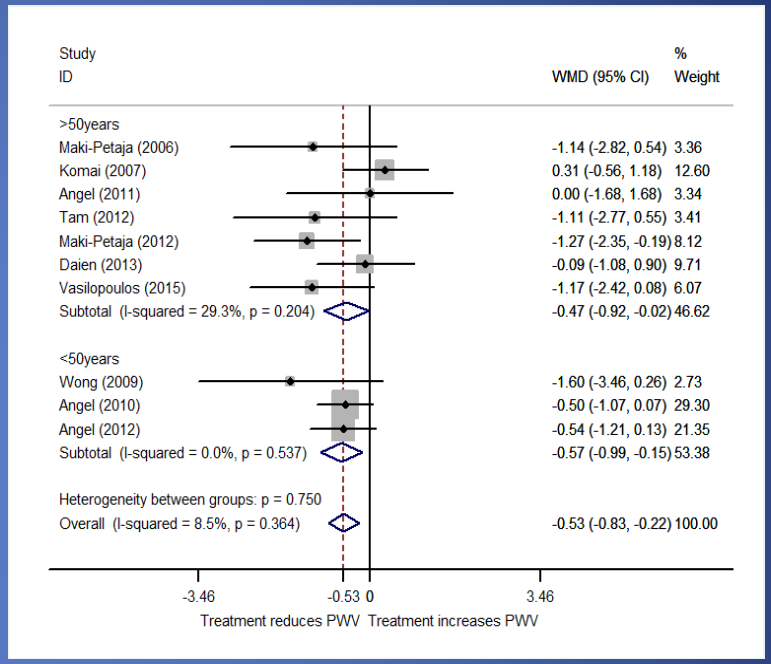
Results



- Subjects that were treated with anti-TNF therapy significantly improved their AIx (mean change: -1.48% [95% confidence intervals: -2.89/-0.078%], z=2.07, p=0.039)
- No significant heterogeneity was observed across the studies (I^2=0.0 , p=0.768)

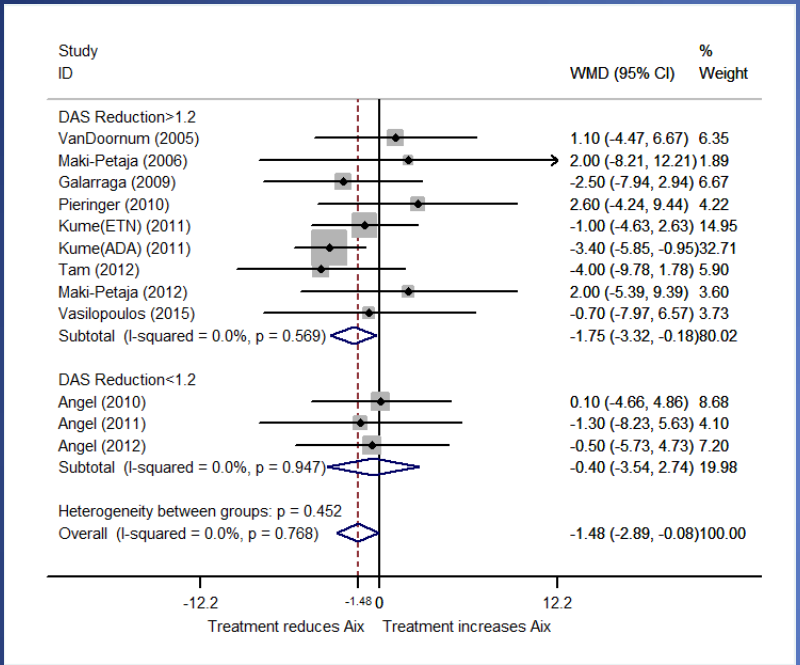
Results

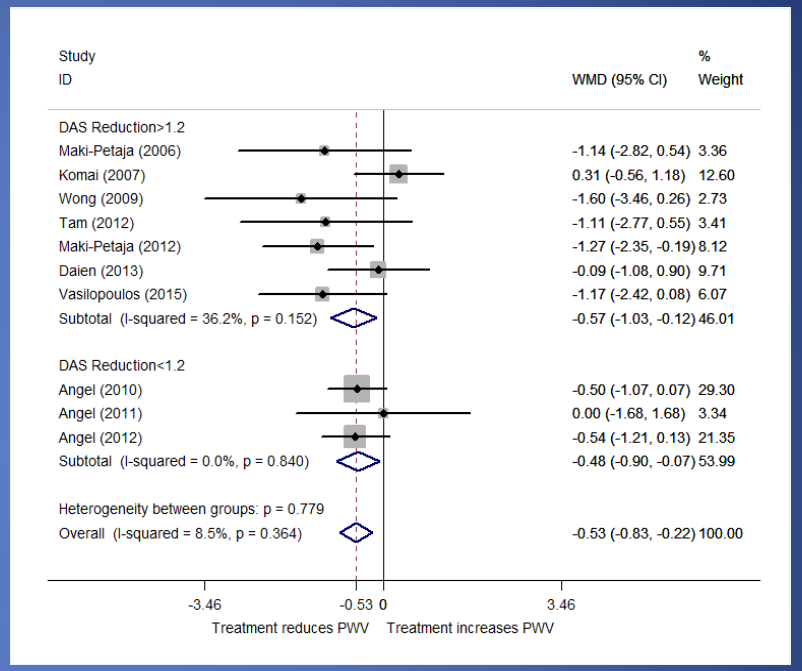




- By subgroup analysis, improvement in AIx and PWV after therapy was independent from age and sex.

Results



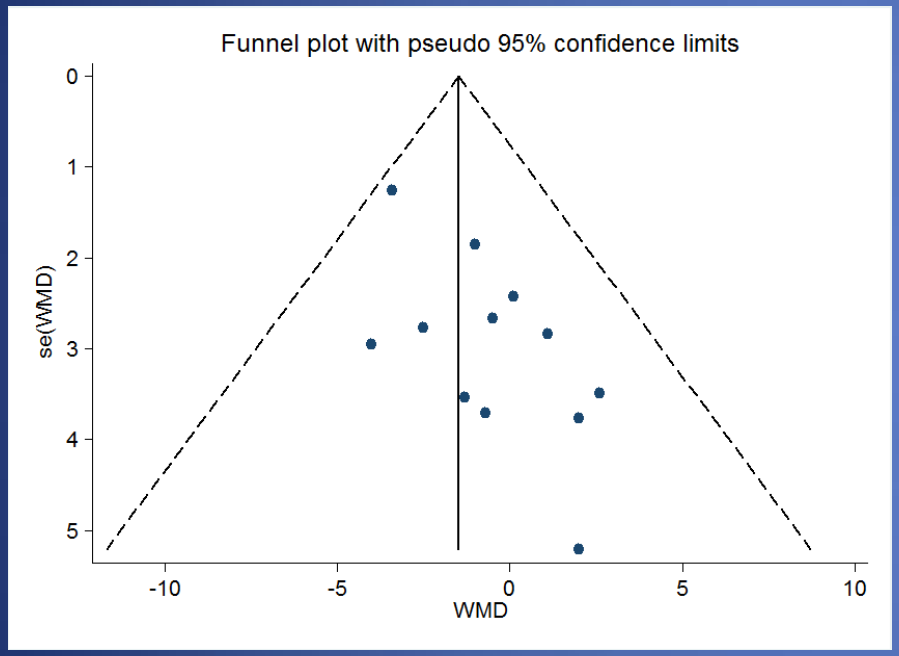


- By subgroup analysis, improvement in AIx and PWV after therapy was independent from clinical response to treatment [DAS reduction>1.2].

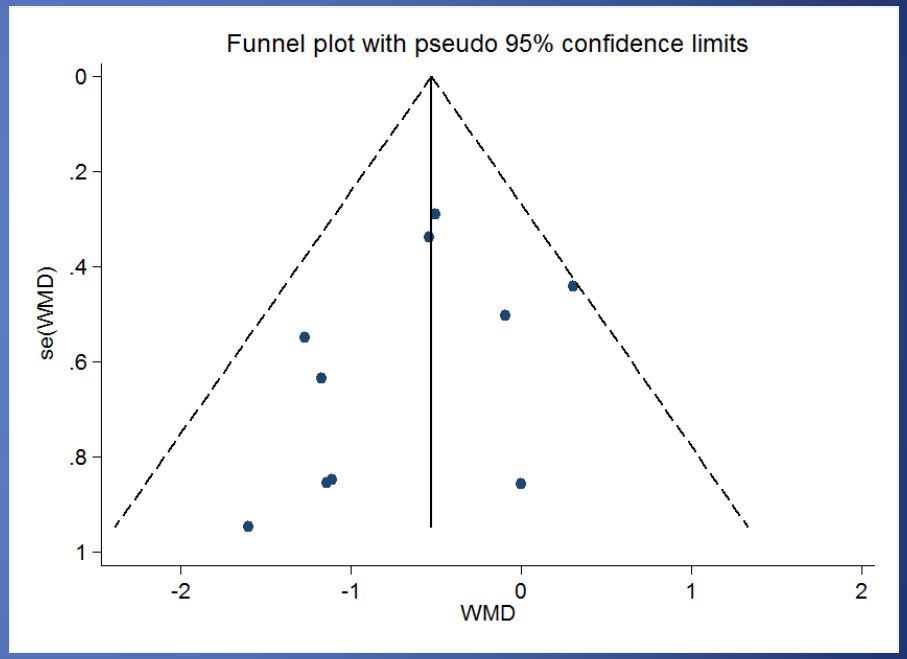
Publication bias

Funnel plots

AIx



PWV



- The funnel plot for PWV (and to less extent for AIx) was rather symmetrical suggesting that publication bias is not sufficient to influence our findings in a meaningful way.

Limitations

- Use of aggregate –summary- data (no data of individual patients)
- Small number of patients and studies
- Short period of treatment (3 months)
- The absence of a direct control group

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Conclusions

- TNF-a inhibitors may have a favorable effect on arterial stiffness and wave reflections.
- It remains unknown whether this effect is specific to TNF-a antagonists or relates to better control of inflammation irrespective of the disease modification strategy by which this is achieved.
- However, longer-term cohort studies are needed to confirm these promising results.

Thank you for your attention