Tumor Necrosis Factor-α Antagonists Improve Aortic Stiffness in Patients With Inflammatory Arthropathies
A Controlled Study

Kristin Angel, Sella Aarrestad Provan, Hanne Løvdahl Gulseth, Petter Mowinckel, Tore Kristian Kvien, Dan Atar

Abstract—The chronic inflammatory state of rheumatoid arthritis and other inflammatory arthropathies, such as ankylosing spondylitis and psoriatic arthritis, contributes to the accelerated atherosclerosis associated with these conditions. This study evaluates the effect of treatment with tumor necrosis factor (TNF-α) antagonists on arterial stiffness in patients with inflammatory arthropathies. A total of 60 patients with rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis and clinical indication for anti-TNF-α therapy were included. Thirty-five patients started with anti-TNF-α therapy and were compared with a nontreatment group of 25 patients. Aortic stiffness (aortic pulse wave velocity), augmentation index, and disease activity were assessed at baseline and after 3 months. Aortic pulse wave velocity (mean±SD) was reduced in the treatment group but not in the control group (−0.50±0.78 m/s versus 0.05±0.54 m/s, respectively; \(P=0.002\)). Concomitantly, C-reactive protein and the disease activity score were reduced in the treatment group (−9.3±20.2 mg/L \(P<0.001\) and −0.74±0.91 \(P=0.004\)). Augmentation index remained unchanged in both groups (0.1±7.1% versus −1.0±5.8%, respectively; \(P=0.53\)). In a multivariate linear regression model, only treatment with TNF-α antagonist and change in mean arterial pressure predicted alterations in aortic pulse wave velocity. In summary, anti-TNF-α therapy improved aortic stiffness in patients with inflammatory arthropathies. These findings support the idea that anti-inflammatory treatment has a favorable effect on cardiovascular risk in patients with inflammatory arthropathies. (Hypertension. 2010;55:333-338.)

Key Words: atherosclerosis ■ inflammation ■ vasculature ■ arthritis rheumatoid ■ arterial stiffness

Patients with rheumatoid arthritis (RA) or other inflammatory arthropathies, such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), have an increased risk of cardiovascular disease.¹-⁴ The excess risk cannot be fully accounted for by traditional risk factors, and several studies have indicated that the systemic inflammatory burden in inflammatory arthropathies accelerates atherosclerosis.⁵,⁶ Endothelial dysfunction, increased arterial stiffness, and intima media thickness are independent predictors of cardiovascular disease⁵-⁹ and are demonstrated to be abundantly present in patients with RA when compared with healthy control subjects.¹⁰-¹² Some recently published reports indicate that patients with AS and PsA also have impaired endothelial function¹³,¹⁴ and increased intima-media thickness,¹⁵,¹⁶ but data regarding the association between these diseases and premature atherosclerosis are still limited.

Access to anti-tumor necrosis factor-α (TNF-α) therapy has become a major advance in the treatment of RA, AS, and PsA over the last 10 years.¹⁷ TNF-α is an important proinflammatory cytokine, involved in the synovitis of patients with RA, AS, and PsA, but also in the atherosclerotic progression.¹⁸ Other than improving the clinical outcome in inflammatory arthropathies, anti-TNF-α treatment may, therefore, have favorable effects on the cardiovascular system. Indeed, reports from Swedish and British biological registers indicate that anti-TNF-α therapy reduces the incidence of cardiovascular events in patients with RA.¹⁹,²⁰ Moreover, treatment with TNF-α antagonists is reported by a few small studies to improve endothelial function and aortic stiffness in patients with RA¹¹,¹²,²¹ and microvascular function in patients with AS.¹⁴ Aortic pulse wave velocity (aPWV), a measure of aortic stiffness, is considered the current gold standard for measuring arterial stiffness.⁹ The effect of treatment with TNF-α antagonists on aPWV in other inflammatory arthropathies than RA was, to our knowledge, not explored previously. Furthermore, existing studies have not included a control group or have compared with healthy controls, not taking into consideration the natural fluctuations in inflammatory activity that occur in RA, AS, and PsA. Thus, the objective of the current study was to evaluate the effect of anti-TNF-α therapy on aPWV and augmentation index (AIx), a measure of pulse wave reflection, in patients with RA, AS, and PsA compared with a nontreatment group of patients with similar inflammatory activity and, furthermore, to explore possible associations between changes in inflammatory activity and changes in the vascular parameters.

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Patients and Methods

Design and Patients
Sixty patients with RA, AS, or PsA were recruited from the 2 major rheumatology outpatient clinics in the Oslo area. All of the patients had active inflammatory disease and clinical indication for anti-TNF-α therapy. Fifty-eight patients were TNF-α antagonist naive; 2 patients had previously (>18 months before inclusion) used a TNF-α antagonist but had ended treatment because of failure or allergic reaction. The treatment group consisted of the 35 patients who started with TNF-α antagonists without delay (16 with adalimumab, 13 with etanercept, and 6 with infliximab), whereas the control group was composed of 25 patients who fulfilled the same indication for anti-TNF-α therapy as the patients in the treatment group but had to postpone their therapy initiation because of a positive Mantoux test, their working situation, or planned operations. Patients with arterial hypertension, defined as systolic pressure ≥140 mm Hg, diastolic pressure ≥90 mm Hg, or current use of antihypertensive medication, had to be well controlled according to the European Society of Hypertension/European Society of Cardiology guideline treatment targets (systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg) for ≥6 months before the study start, and antihypertensive medication could not be changed during the study period. Patients on lipid-lowering treatment could only be included if they had been stable on the same dose ≥6 months before inclusion and a change in dose during the study period would lead to exclusion. Both the anti-TNF-α group and the control group underwent measurements of arterial stiffness at baseline and after 3 months. Core measures of disease activity were assessed, and fasting blood samples were drawn at each examination. Approval was obtained from the regional research ethics committee, and written informed consent was obtained from each participant. The study was performed according to the Helsinki declaration.

Measurements of Arterial Stiffness
The patients were examined in a quiet, temperature-controlled room after an overnight fast including abstinence from tobacco, alcohol, tea, and coffee. Systolic and diastolic blood pressures were measured in the brachial artery with a validated automated device (Omron HEM-757). Blood pressure measurements were taken with an appropriately sized cuff after the patient had been relaxed for 10 minutes in a supine position. The same arm was used for measurement at each visit. 3 measurements were performed, and the average was used as brachial blood pressure.

aPWV and Alx were assessed with the SphygmoCor device version 7.1 (AtCor Medical). To obtain the Alx, peripheral pressure waveforms were recorded from the radial artery at the wrist with a validated tonometer (SPC-301, Millar Instruments). Corresponding central aortic waveforms were generated by integrated software, from which central hemodynamics and aortic Alx were calculated. Mean arterial pressure (MAP) was determined from the pressure waveform and the femoral site of recording. All of the Alx and aPWV measurements were made in triplicate by the same examiner (K.A.), and the mean values were used in the analyses. The examiner did not participate in the treatment of the rheumatic disease, and information of the patient treatment was gathered after the data collection and the analyses of the measurements were finished.

Disease Activity
The clinical status and disease activity were evaluated according to the American College of Rheumatology preliminary core set of disease activity measures for RA clinical trials. This included the Health Assessment Questionnaire, visual analog scales, and acute-phase reactants for all of the patients. In addition, the disease activity score on the basis of 28 joints (DAS28) and erythrocyte sedimentation rate (ESR) were recorded in the patients with RA.

Laboratory Measurements
ESR was analyzed by the Westergren method, and hemoglobin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein (CRP), and creatinine were determined by standard methodology (Sysmex Corporation and Roche Diagnostics GmbH).

Statistical Analysis
Data are presented as mean±SD or as median with interquartile range in the situation of not normally distributed variables. Continuous variables were compared using the Student t test for independent samples or Mann–Whitney U test when appropriate. For within-group changes, paired Student t tests or Wilcoxon signed-rank tests were performed. Categorical variables were compared using the Pearson χ² test. Bivariate relations were analyzed using a Spearman correlation coefficient. Predictors of the baseline value and change in aPWV were explored using ANCOVA with CRP and change in CRP as both a continuous variable and categorized into quartiles. Furthermore, for determinants of the change in aPWV, a robust multiple stepdown regression analysis was performed because of nonnormality of the residuals. Variables significant at the P=0.25 level in the bivariate analyses were entered into the regression model with aPWV as the dependent variable. Variables were then removed in a stepdown manner described by Hosmer and Lemeshow. The model was examined for relevant interactions and confounding in a standard manner. In addition, we did a 1 to 1 matching of the 25 patients in the control group with 25 patients in the treatment group by age, sex, and MAP. In the matched-pairs analysis, a 2-way ANOVA with randomized blocks was applied. The magnitude of the response at 3 months in aPWV and key inflammatory measures in the 2 patient groups were compared with standardized response mean (SRM) values (mean change from baseline/SD of the change). SRM values were interpreted as effect sizes according to Cohen. SRMs and <0.5, ≥0.5 and <0.8, and ≥0.8 indicate small, moderate, and large magnitudes of change, respectively. P≤0.05 was considered significant. Statistical analyses were performed with SPSS version 16.0 (SPSS Inc) and R (R Development Core Team, 2008: R: a language and environment for statistical computing, R Foundation for Statistical Computing).

Results
The 2 patient groups did not differ at baseline with regard to age, sex, disease duration, rheumatic diagnosis, comorbidities, smoking habits, or current antirheumatic medication (Table 1). None of the patients had prediagnosed diabetes
mellitus or used antidiabetic medication. According to the protocol, none of the patients changed antihypertensive or lipid-lowering therapy. Antiheumatic medication beyond anti–TNF-α antagonists remained unchanged in the 2 groups throughout the study period.

Comparison of baseline measurements and changes at 3-month follow-up for the cardiovascular variables are presented in Table 2. The 2 patient groups had similar baseline values for aPWV, AIX, peripheral and central brachial systolic and diastolic blood pressures, MAP, and heart rate. The aPWV decreased significantly after 3 months of anti–TNF-α therapy but remained unchanged in the control group. The magnitude of reduction in aPWV was not significantly different among the patients with RA, AS, or PsA (aPWV was not significantly different among the patients with RA, AS, or PsA (Table 2). As expected, most disease activity and health status variables improved in the treatment group after 3 months with anti–TNF-α therapy and did not change in the control group (Table 3). The reduction in DAS28 (RA patients only) and Health Assessment Questionnaire score in the treatment group did not reach statistical significance when compared with the control group. However, within the treatment group, DAS28 and Health Assessment Questionnaire were also significantly reduced (−0.74 ± 0.91 [P = 0.004] and −0.21 ± 0.36 [P = 0.001]). As for the other biochemical variables, hemoglobin increased

### Table 2. Baseline Measurements and Changes in Cardiovascular Variables From Baseline to 3-Month Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (Anti-TNF n=35)</th>
<th>Baseline (Control n=25)</th>
<th>P</th>
<th>Change (Anti-TNF n=35)</th>
<th>Change (Control n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>129.8 ± 20.5</td>
<td>132.0 ± 17.0</td>
<td>0.65</td>
<td>−2.5 ± 9.5</td>
<td>−2.6 ± 10.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>79.1 ± 10.7</td>
<td>79.2 ± 8.7</td>
<td>0.97</td>
<td>−2.4 ± 7.1</td>
<td>−2.1 ± 7.4</td>
<td>0.91</td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td>120.6 ± 20.5</td>
<td>121.7 ± 17.5</td>
<td>0.83</td>
<td>−2.5 ± 9.5</td>
<td>−3.5 ± 9.6</td>
<td>0.70</td>
</tr>
<tr>
<td>Central PP, mm Hg</td>
<td>41.5 ± 14.2</td>
<td>41.2 ± 12.0</td>
<td>0.93</td>
<td>−1.0 ± 7.8</td>
<td>−1.4 ± 6.6</td>
<td>0.85</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>97.1 ± 13.7</td>
<td>97.7 ± 12.1</td>
<td>0.87</td>
<td>−2.1 ± 7.9</td>
<td>−2.6 ± 7.8</td>
<td>0.80</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>64.9 ± 10.0</td>
<td>63.1 ± 9.7</td>
<td>0.48</td>
<td>−0.2 ± 9.1</td>
<td>2.0 ± 9.3</td>
<td>0.37</td>
</tr>
<tr>
<td>Central AP, mm Hg</td>
<td>9.6 ± 7.3</td>
<td>8.4 ± 6.5</td>
<td>0.52</td>
<td>0.7 ± 3.4</td>
<td>0.6 ± 3.1</td>
<td>0.91</td>
</tr>
<tr>
<td>AIX, %</td>
<td>23.0 ± 12.4</td>
<td>19.8 ± 12.5</td>
<td>0.33</td>
<td>0.1 ± 7.1</td>
<td>−1.0 ± 5.8</td>
<td>0.53</td>
</tr>
<tr>
<td>aPWV, m/s</td>
<td>7.45 ± 1.44</td>
<td>7.47 ± 1.29</td>
<td>0.96</td>
<td>−0.50 ± 0.78</td>
<td>0.05 ± 0.54</td>
<td>0.002</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; AP, augmentation pressure; HR, heart rate. Values are represented as mean ± SD. *Data show RA patients only.

### Table 3. Baseline Values and Changes in Disease Activity and Biochemical Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (Anti-TNF n=35)</th>
<th>Baseline (Control n=25)</th>
<th>P</th>
<th>Change (Anti-TNF n=35)</th>
<th>Change (Control n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L</td>
<td>8.0 (1.9,15.0)</td>
<td>6.0 (2.8,14.0)</td>
<td>0.81</td>
<td>−2.2 (−8.3,0.0)</td>
<td>1.5 (−1.5,−6.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>16.0 (6.0,30.0)</td>
<td>16.0 (10.5,31.0)</td>
<td>0.66</td>
<td>−4.0 (−12.0,−1.0)</td>
<td>3.0 (−3.0,9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAS p global, mm</td>
<td>50.0 ± 22.5</td>
<td>42.0 ± 19.5</td>
<td>0.11</td>
<td>−21.0 ± 23.6</td>
<td>−19.0 ± 18.9</td>
<td>0.001</td>
</tr>
<tr>
<td>VAS i, global mm</td>
<td>42.9 ± 11.6</td>
<td>38.4 ± 13.3</td>
<td>0.18</td>
<td>−15.3 ± 12.8</td>
<td>−2.4 ± 10.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.91 ± 0.55</td>
<td>0.66 ± 0.51</td>
<td>0.11</td>
<td>−0.21 ± 0.36</td>
<td>−0.02 ± 0.25</td>
<td>0.14</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>13.4 ± 1.4</td>
<td>13.9 ± 1.3</td>
<td>0.19</td>
<td>0.5 ± 0.8</td>
<td>−0.1 ± 0.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>63.5 ± 16.2</td>
<td>74.7 ± 12.2</td>
<td>0.01</td>
<td>3.9 ± 9.9</td>
<td>1.45 ± 8.0</td>
<td>0.32</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.74 ± 0.79</td>
<td>5.22 ± 0.95</td>
<td>0.05</td>
<td>0.41 ± 0.93</td>
<td>0.18 ± 0.56</td>
<td>0.26</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.67 ± 0.81</td>
<td>3.16 ± 0.82</td>
<td>0.04</td>
<td>0.21 ± 0.71</td>
<td>0.09 ± 0.48</td>
<td>0.47</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.53 ± 0.38</td>
<td>1.49 ± 0.53</td>
<td>0.71</td>
<td>0.09 ± 0.29</td>
<td>−0.04 ± 0.26</td>
<td>0.08</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.12 ± 0.52</td>
<td>1.21 ± 0.05</td>
<td>0.52</td>
<td>0.34 ± 0.61</td>
<td>0.23 ± 0.75</td>
<td>0.55</td>
</tr>
</tbody>
</table>

VAS indicates visual analogue scale (patient [P] and investigator [I] evaluation of global disease activity); HAQ, Health Assessment Questionnaire; Hb, hemoglobin; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides. Values are represented as mean ± SD, except for CRP and ESR, which were skewed and are represented as median (interquartile range).

*Data show RA patients only.
significantly in the treatment group after 3 months. Creatinine, total cholesterol, and high-density lipoprotein cholesterol were lower in the treatment group at baseline, but there were no differences in the changes in lipids or kidney function between the groups (Table 3).

aPWV and AIx were not correlated with the disease activity variables at baseline, even after adjustment for age, sex, and MAP. Furthermore, we did not find any significant bivariate correlations between the changes in aPWV and CRP (ρ = 0.13; P = 0.43), ESR (ρ = 0.13; P = 0.31), or DAS28 (RA patients; ρ = −0.15; P = 0.59) in the treatment group. However, when change in CRP was categorized into quartiles, patients with the largest reduction in CRP had a significantly greater reduction in aPWV after 3 months than the patients in the lowest quartile (−0.63±0.75 m/s versus 0.06±0.60 m/s, respectively; P = 0.01), but the overall model was not significant (P = 0.08). The change in aPWV and the inflammatory markers in the 2 patient groups were further compared with SRM that demonstrated a moderate-to-high responsiveness (SRM: >0.50) in aPWV, CRP, ESR, and DAS28 to anti–TNF-α therapy (Figure).

In the stepdown multiple regression analysis with change in aPWV as a dependent variable, only treatment versus no treatment with TNF-α antagonist and change in MAP remained in the model as independently associated variables (Table 4). Neither changes nor baseline levels of any of the biochemical variables, disease activity variables, or HR remained in the final model. Moreover, duration of the inflammatory disease, diagnosis of inflammatory arthropathy, type of TNF-α antagonist, use of other medication than TNF-α antagonists, and comorbidities did not influence change in aPWV. Age and sex did not significantly predict change in aPWV but were kept in the model for adjustment. After matching the patients by age, sex, and MAP, anti–TNF-α treatment remained a significant predictor of change in aPWV, whereas change in MAP only tended to be significant (Table 5).

### Discussion

Previous findings indicate that the inflammatory activity in RA, AS, and PsA accelerates atherosclerosis. The present study demonstrates that anti–TNF-α treatment reduces inflammatory activity and improves aortic stiffness in patients with inflammatory arthropathies (Figure). This effect was consistent in a regular comparative analysis (Table 2), as well as in a multivariate analysis, with treatment group as an independent and aPWV as a dependent variable (Tables 4 and 5). Our findings are in line with a few previous reports of improvement in endothelial function and aortic stiffness in patients with RA11,22 after initiation of anti–TNF-α therapy. Maki-Petaja et al11 showed a reduction in aPWV and flow-mediated dilatation to the level of healthy controls in a group of 9 patients with RA, whereas Hurlimann et al21 and Wong et al22 demonstrated within-treatment group improvements in vascular function. The novel approach of the current study was to compare the treatment group with a nontreatment group of patients with similar inflammatory activity as those receiving anti–TNF-α therapy. Furthermore, we included a larger number of patients than previous studies and demonstrated for the first time that anti–TNF-α therapy improves aortic stiffness in patients with AS and PsA.

We did not find any changes in AIx after 3 months of anti–TNF-α therapy. Although one recently published study reported that treatment with etanercept reduced AIx,31 our result is in agreement with the majority of previous investigations exploring the effect of TNF-α antagonists on AIx.11,16,22,32 AIx is a composite measure dependent on the magnitude and site of pulse wave reflection in addition to the speed of the reflected wave. Peripheral vasodilatation is a well-known feature of infectious diseases, such as septicemiae, induced among others by TNF-α. A normalization of the vasculature tonus subsequent to the antiinflammatory treatment and, thus, an increase in the magnitude of the pulse wave reflection, may explain why the AIx remained unchanged in the current study despite the reduction in aPWV. In support to this explanation, Irace et al33 have demonstrated that treatment with etanercept reduced AIx, whereas Hurlimann et al21 and Wong et al22 demonstrated within-treatment group improvements in vascular function. The novel approach of the current study was to compare the treatment group with a nontreatment group of patients with similar inflammatory activity as those receiving anti–TNF-α therapy. Furthermore, we included a larger number of patients than previous studies and demonstrated for the first time that anti–TNF-α therapy improves aortic stiffness in patients with AS and PsA.

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The patients in the present study receiving anti–TNF-α therapy had, as expected, a significant reduction in inflammatory measures (Table 3). CRP, ESR, DAS28, and aPWV

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**Table 4. Stepwise Multiple Regression Analysis for Change in aPWV (n=60)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>−0.020 (−0.340, 0.299)</td>
<td>0.90</td>
</tr>
<tr>
<td>Age, y</td>
<td>−0.002 (−0.015, 0.011)</td>
<td>0.74</td>
</tr>
<tr>
<td>Anti-TNF-α therapy</td>
<td>−0.465 (−0.789, −0.165)</td>
<td>0.003</td>
</tr>
<tr>
<td>Δ MAP, mm Hg</td>
<td>0.029 (0.008, 0.050)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure.
all showed a moderate-to-high responsiveness to anti–TNF-α therapy, as demonstrated with SRM (Figure). Aortic stiffness has been demonstrated previously in cross-sectional examinations to correlate with disease duration and/or markers of inflammation in patients with RA.\textsuperscript{11,35} We could not demonstrate any significant correlations between baseline values or changes in aPWV and biochemical or clinical inflammatory markers, although there was a clear trend toward a correlation between changes in CRP and aPWV. Thus, our findings may very well be type II errors because of the size of the patient population. However, existing studies also report a parallel reduction in measurements of aPWV and CRP during anti–TNF-α therapy, but no correlation.\textsuperscript{22} This may indicate that CRP does not completely reflect the effects of TNF-α inhibition in the artery wall. Elevated plasma levels of CRP are evidently associated with increased risk of cardiovascular disease; however, recent results indicate that CRP is marker but not a causal factor for atherosclerosis and cardiovascular disease.\textsuperscript{36} Hence, other inflammatory mediators not measured in this study may correlate better with changes in aPWV.

Inflammation may promote cardiovascular disease through advancing endothelial dysfunction, arterial stiffness, and atherosclerotic lesions directly but also by accentuation of traditional risk factors, such as serum lipids, insulin resistance,\textsuperscript{37} or blood pressure.\textsuperscript{38} Patients with RA have been demonstrated to exhibit an unfavorable lipid profile and an increased prevalence of hypertension.\textsuperscript{39} Interestingly, cholesterol-lowering therapy reduces inflammatory markers,\textsuperscript{40} endothelial dysfunction, and aortic stiffness in patients with RA.\textsuperscript{41} Data regarding the effect of anti–TNF-α therapy on serum lipid levels have been inconsistent, but it seems overall that this treatment does not have any major influence on standard serum lipid levels,\textsuperscript{42} although it may improve the anti-inflammatory capacity of high-density lipoprotein.\textsuperscript{43} Anti–TNF-α therapy is, thus far, not reported to affect blood pressures in patients with inflammatory arthropathies.\textsuperscript{22,39} We did not find any change in blood pressures, standard serum lipids, liver function, or kidney function. We demonstrated a significant increase in hemoglobin (0.5 g/dL) in the treatment group, but this result did not enter the final multivariate regression model for determinants of change in aPWV (Table 4). Thus, our findings support previous results of a favorable effect of anti-inflammatory treatment on cardiovascular risk in patients with inflammatory arthropathies that is beyond the influence on traditional cardiovascular risk factors.\textsuperscript{20,44}

The present study has several limitations. An optimal design would have been to perform a randomized, controlled clinical trial. However, we did not find this design ethically acceptable, because the baseline characteristics of the patients confirm that all of the patients had a clear clinical indication for treatment with TNF-α antagonists according to Norwegian guidelines. Previous studies have also used an open-label design.\textsuperscript{11,21,22} Obviously, our choice of control group could introduce potential bias. Patients in the treatment group could tend to have a more severe disease that was not detectable by our disease activity measurements. However, this would be expected to bias toward the null hypothesis. Furthermore, several patients in the control group were Mantoux positive. Although none of them had symptoms, they could have had a silent mycobacterial infection. However, further examinations did not confirm disease in any of the patients. Thus, it seems unlikely that this influenced our results. Three types of inflammatory arthropathies were included in the study, which makes the total population more heterogeneous. We also included all 3 types of available anti–TNF-α treatment, and even if they all target TNF-α, they differ somewhat in their mechanism of action. However, the numeric effect on PWV was rather similar, both for the different diagnoses and for different anti–TNF-α drugs.

**Perspectives**

The present study shows that anti–TNF-α therapy improves aPWV in patients with inflammatory arthropathies, including also AS and PsA. The effect of anti–TNF-α therapy on aortic stiffness was robust, because it was consistent with 2 different analytical approaches. These findings support the notion of a favorable effect of anti-inflammatory treatment on cardiovascular risk in patients with inflammatory arthropathies.

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**References**


