Patients with coronary artery disease (CAD) and rheumatoid arthritis (RA) present similar inflammatory pathways leading to atherogenesis. A common pathway is increased interleukin-1 (IL-1) production, triggering oxidative stress and leading to vascular and myocardial injury. However, it is not clear whether this pathway is more active in patients with CAD and coexistent RA.

Anakinra, a recombinant form of human IL-1 receptor antagonist, is used for the treatment of RA. Anakinra has been shown to reduce myocardial injury in other states where IL-1 is elevated. Thus, the drug reduced experimental myocardial infarction and improved left ventricular (LV) volumes, as assessed by MRI after myocardial infarction in non-RA patients. LV myocardial deformation, twisting, and untwisting, as assessed by speckle tracking echocardiography, are major determinants of LV remodeling and prognosis after myocardial infarction. In our previous studies of patients with RA with normal LV ejection fraction (EF) and no evidence of CAD, we have documented the acute beneficial effects of anakinra on vascular and LV function. However, the acute effects of anakinra treatment on vascular function, LV deformation, and twisting in patients with CAD and coexistent RA have not been studied.

### Background
We investigated the effects of anakinra, an interleukin-1 receptor antagonist, on coronary and left ventricular function in coronary artery disease (CAD) patients with rheumatoid arthritis.

### Methods and Results
In a double-blind crossover trial, 80 patients with rheumatoid arthritis (60 with CAD and 20 without) were randomized to a single injection of anakinra or placebo and after 48 hours to the alternative treatment. At baseline and 3 hours after treatment, we assessed (1) flow-mediated dilation of brachial artery; (2) coronary flow reserve, ejection fraction, systemic arterial compliance, and resistance by echocardiography; (3) left ventricular global longitudinal and circumferential strain, peak twisting, untwisting velocity by speckle tracking; and (4) interleukin-1β, nitrotyrosine, malondialdehyde, protein carbonyl, and Fas/Fas ligand levels. At baseline, patients with CAD had 3-fold higher interleukin-1β, protein carbonyl, higher nitrotyrosine, malondialdehyde, and Fas/Fas ligand than non-CAD patients ($P<0.05$). After anakinra, there was a greater improvement of flow-mediated dilation (57±4% versus 47±5%), coronary flow reserve (37±4% versus 29±2%), arterial compliance (20–18% versus 2±17%), resistance (−11±19% versus 9±21%), longitudinal strain (33±5% versus 18±2%), circumferential strain (22±5% versus 13±5%), peak twisting (30±5% versus 12±5%), untwisting velocity (23±5% versus 13±5%), ejection fraction (12±5% versus 0.5±5%), apoptotic and oxidative markers, and, in particular, of protein carbonyl (35±20% versus 14±9%) in CAD than in non-CAD patients ($P<0.01$). No changes in the examined markers were observed after placebo.

### Conclusions
Interleukin-1 inhibition causes a greater improvement in endothelial, coronary aortic function in addition to left ventricular myocardial deformation and twisting in rheumatoid arthritis patients with CAD than in those without.

### Clinical Trial Registration

### Key Words:
coronary artery disease, interleukin-1, interleukin-1 receptor antagonist protein, oxidative stress
myocardial deformation, and, in particular, on LV twisting–untwisting properties have not been evaluated in patients with RA with and without CAD separately.

In the present study, we hypothesized that patients with CAD and coexistent RA have higher IL-1 activity and oxidative burden than those without. Therefore, IL-1 inhibition by anakinra would have a greater benefit on vascular and myocardial function in patients with CAD compared with non-CAD patients through reduction of a larger IL-1–driven oxidative stress and myocardial cell damage.

Thus, in the present study, we explored the effects of anakinra on (1) markers of oxidative stress and apoptosis as assessed by malondialdehyde, nitrotyrosine, protein carbonyls (PC), and Fas/Fas ligand blood levels; (2) vascular function as assessed by flow-mediated dilatation (FMD) of the brachial artery, coronary flow reserve, arterial compliance, and resistance; and (3) LV myocardial function, deformation, twisting, and untwisting as assessed by 2-dimensional (2D) and speckle tracking–derived echocardiographic indices in RA patients with CAD compared with those without.

Methods

Study Population

We recruited 60 patients with RA (American Rheumatism Association criteria) with angiographically documented chronic stable CAD (≥70% luminal diameter stenosis) and that were matched by age and sex with 20 patients with RA without evidence of CAD (Table 1). All patients were on methotrexate 7.5 mg once per week, leflunomide 20 mg OD, and prednisolone 5 mg OD.

Exclusion criteria were acute coronary syndrome within the past year, familial hyperlipidemia, insulin-dependent diabetes mellitus, chronic obstructive pulmonary disease or asthma, moderate or severe valvular heart disease, primary cardiomyopathies, and malignant tumors. CAD was excluded by the absence of clinical history, angina, and reversible myocardial ischemia, as assessed by dobutamine stress echocardiography or thallium scintigraphy.

None of our patients were on treatment with nonsteroidal anti-inflammatory drugs within the past year. All patients were on a stable dosage of statins and cardioactive medications for the past 6 months. We calculated the composite inflammatory disease activity score that includes systemic arterial compliance.

Thirty asymptomatic subjects with similar age, sex, and atherosclerotic risk factors as the patients with RA, with a normal ECG, echocardiogram, and treadmill test, were selected as control subjects among subjects attending the cardiology outpatients’ clinic.

Study Protocol

In a double-blind, placebo-controlled trial, all patients were randomized to receive a single injection of anakinra, a recombinant IL-1 receptor antagonist (100 mg SC) or placebo. After 48 hours, patients were crossed over to the alternate treatment (placebo or anakinra), and measurement of the examined markers was repeated. The 48-hour interval between the 2 consecutive studies was decided to secure a sufficient washout period of anakinra in accordance with the drug’s half-life time (ranging between 4 and 6 hours).21 A single subcutaneous injection of 100 mg of anakinra results in (1) 95% bioavailability, (2) mean peak IL-1 receptor antagonist blood levels of 1.2 to 1.35 μg/mL after 3 to 5 hours followed by a rapid decrease to 0.035 μg/mL after 24 hours, and (3) a rapid clinical and biochemical response within 4 and 24 hours, respectively.22

The dosage of vasoactive medication (β-blockers, calcium channel antagonists, and nitrates) had been reduced to half for an additional period of 24 hours to avoid a rebound effect and to monitor the frequency of angina before complete drug cessation for another 24-hour period. Patients were instructed to use short-acting nitrates in case of an anginal episode. None of the patients was excluded because of exacerbation of angina.

At baseline and 3 hours after the single injection, we performed blood sampling and ultrasonography for the assessment of biomarkers and markers of vascular and LV function. The control subjects had a single baseline measurement of all examined markers. The study protocol was approved by the Institute’s Ethics Committee, and written informed consents were obtained from all patients.

Echocardiography

Studies were performed using a Vivid 7 (GE Medical Systems, Horten, Norway) ultrasound system. All studies were digitally stored (Echopac GE, Horten, Norway) and analyzed by 2 observers (I.L. and S.T.) blinded to clinical and laboratory data.

Two-Dimensional Echocardiography

We measured the following parameters from 2D echocardiographic images of the LV: end-diastolic volume, end-systolic volume (mL), stroke volume (SV=end-systolic volume−end-systolic volume; mL), and EF (%) using the Simpson method of discs. Segmental wall motion abnormalities (hypokinesis, akinesis, and dyskinesis) were noted.

Systemic Arterial Resistance and Compliance

Systolic blood pressure and diastolic blood pressure were obtained by cuff sphygmomanometry. Pulse pressure and mean blood pressure were calculated as follows: pulse pressure=systolic blood pressure−diastolic blood pressure and mean blood pressure=pulse pressure/3+ diastolic blood pressure. Stroke volume was normalized for body surface area and expressed as SV index (=SV/body surface area). Systemic vascular resistance was calculated according to the formula: systemic vascular resistance=80×(mean arterial pressure−5)/cardiac index (dynes/cm² per m²), where 5 is an approximation of the right atrial pressure and cardiac index=stroke volume index×heart rate.23 Systemic arterial compliance was calculated as stroke volume index/pulse pressure (mL/mmHg per m²).23 Inter- and intraobserver variabilities of these measurements were 4.5% and 2.5% for systemic vascular resistance and 3.1% and 2.2% for systemic arterial compliance.

Two-Dimensional Strain Measurements

Using a dedicated software package (Echopac, GE Medical systems, Horten, Norway), LV strain was measured using speckle tracking analysis. We acquired LV apical 2-, 4-, and 3-chamber views as well as LV short-axis views at the basal and the apical levels. Therefore, the LV twist curve was automatically generated from the software by calculating the difference between apical and basal rotations at each corresponding time point. The peak difference between rotation angles at the apex and base (peak twisting [Tw]), the peak twisting (Tw) velocity (degrees/s), and peak untwisting (UnTw) velocity were measured.24 All variables represent the mean value of measurements taken in 3 consecutive cardiac cycles.

The inter- and intraobserver variabilities of LongSR were 8% and 11%; LongSR, 8.3% and 10.2%; CircS, 10.1% and 11.9%; CircSR, 11.1% and 12%; Tw, 8% and 11.1%; Tw velocity, 8.2% and 10.7%; and UnTw velocity, 9.6% and 11.9%, respectively.

Myocardial Velocity Measurements

Using tissue Doppler imaging, we calculated the mean value of systolic and early and late diastolic velocities (S’, E’, and A’) from the septal, lateral, inferior, and anterior mitral annuli in the apical 4- and 2-chamber views. The ratio of the mitral E wave measured by pulsed-wave Doppler to E’/E was calculated as an index of LV diastolic filling pressures.25
Inter- and intraobserver variabilities of $S', E$, and $E'$ were 0.7% and 1.2%, 1% and 3%, and 0.5% and 1.7%, respectively.

**Coronary Flow**

Coronary flow velocities in the left anterior descending coronary artery were obtained with color-guided pulsed-wave Doppler from long-axis apical projections with a 7-MHz transducer.5 The velocity time integral of the overall coronary flow wave (VTItotal) and its diastolic component (VTId) were measured at baseline and after adenosine infusion (140 μg/kg per minute) for 3 minutes, and the ratio of hyperemic to resting measurements was used to calculate the coronary flow reserve (CFR-VTItotal and CFR-VTId, respectively).5 Inter- and intraobserver variabilities of these measurements were 5% and 2%, respectively.

**Endothelial Function**

FMD and nitrate-induced vasodilatation of the brachial artery were determined according to a previously published methodology.5

### Table 1. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>CAD Patients (n=60)</th>
<th>Non-CAD Patients (n=20)</th>
<th>Controls (n=30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity score</td>
<td>4.7±1</td>
<td>5.1±0.9</td>
<td>...</td>
<td>0.7</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>12 (5–23.5)</td>
<td>11 (1–27.1)</td>
<td>...</td>
<td>0.8</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>9 (5.00–37.82)</td>
<td>11 (6.5–35)</td>
<td>0.23 (0.17–1.45)*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Interleukin-1β, pg/mL</td>
<td>3.8 (2.8–4.8)</td>
<td>0.35 (0.22–0.92)†</td>
<td>0.20 (0.17–0.47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>38.0±28.1</td>
<td>43.0±28.2</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>192.0±59.2</td>
<td>212.1±46</td>
<td>209.1±29.7</td>
<td>0.2</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>120.8±37.5</td>
<td>132.1±40</td>
<td>125.3±39.5</td>
<td>0.3</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>47.4±14.7</td>
<td>66.1±18*</td>
<td>57.8±14.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>136.0±94.8</td>
<td>122.2±46</td>
<td>104.4±39.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.5±18</td>
<td>58±17</td>
<td>57.1±19.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.6±3.5</td>
<td>29.3±7</td>
<td>28.4±2</td>
<td>0.7</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>40 (67%)</td>
<td>14 (70%)</td>
<td>18 (60%)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Risk factors**

- Hypertension: 28 (47%) vs 9 (45%) vs 13 (43%), P = 0.8
- Current Smoking: 22 (37%) vs 8 (40%) vs 10 (33%), P = 0.8
- Dyslipidemia: 25 (41%) vs 7 (35%) vs 14 (47%), P = 0.1
- Previous MI: 28 (47%) vs ... vs ...
- Previous PCI: 18 (30%) vs ... vs ...

**Medication**

- β-blockers: 40 (66%) vs 3 (15%)‡ vs 5 (17%), P<0.001
- Ca++ channel blockers: 15 (25%) vs 5 (25%) vs 10 (33%), P = 0.7
- ACE-I / ARBs: 21 (35%) vs 6 (30%) vs 10 (33%), P = 0.8
- Nitrates: 9 (15%) vs ... vs ...
- Statins: 41 (68%) vs 2 (10%)‡ vs 13 (43%), P<0.001
- Diuretics: 18 (30%) vs 6 (30%) vs 11 (36%), P = 0.7
- Antiplatelets: 60 (100%) vs ... vs ...

**Coronary vessel**

- 1-vessels: 33 (55%) vs ... vs ...
- 2-vessels: 24 (40%) vs ... vs ...
- 3-vessels: 9 (15%) vs ... vs ...
- LV mass index, g/m²: 110.2±46.4 vs 107.1±34.6 vs 108.6±19.6, P = 0.6
- RWT: 0.40±0.07 vs 0.42±0.06 vs 0.40±0.08, P = 0.4
- SBP, mm Hg: 129.0±14.6 vs 127.3±19.8 vs 124.0±8.3, P = 0.5
- DBP, mm Hg: 82.2±11.5 vs 79±11.9 vs 78.3±5.6, P = 0.4

Values for biomarkers and disease duration are median and interquartile range. ARB indicates angiotensin receptor blocker; ACE-I, angiotensin-converting enzyme inhibitors; CAD, coronary artery disease; CRP, C-reactive protein; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; RWT, relative wall thickness; and SBP, systolic blood pressure.

By ANOVA using post hoc analysis with Bonferroni correction, we obtained the following P values: *P<0.05 for controls vs CAD and non-CAD; †P<0.05 for CAD vs non-CAD and controls. P value for comparisons among CAD, non-CAD patients, and controls by ANOVA for continuous variables or by contingency table for categorical variables: ‡P<0.05 for CAD vs non-CAD.
Inter- and intraobserver variabilities of the brachial artery diameter were 0.08±0.19 and 0.1±0.12 mm, and the day-to-day variability of FMD was 1.1±1.5.

Laboratory Assays
C-reactive protein was measured by a high-sensitivity particle-enhanced immunonephelometry (Dade Behring, Marburg, Germany; measurement range, 0.175–30 mg/L). An ELISA was used to determine nitrotyrosine (Hycut Biotechnology bv, Uden, The Netherlands; measurement range, 2–400 nmol/L). Malondialdehyde was determined spectrophotometrically with a commercial kit (Oxford Biomedical Research, Rochester Hills, MI, colorimetric assay for lipid peroxidation; measurement range, 1–20 nmol/L). For the quantification of PC content, we based on spectrophotometric measurement of 2,4-dinitrophenylhydrazine derivatives of PC, as previously published, and results are expressed as nmol/mg protein. Concentrations of IL-1β, Fas-L, and Fas were measured using ELISA kits (for IL-1β: high sensitivity, R&D Systems; method sensitivity: 0.023–0.140 pg/mL; for Fas-L: Diaclone, Cedex; method sensitivity <12 pg/mL; and for Fas: Diaclone, Cedex; method sensitivity <47 pg/mL).

Statistical Analysis
We planned to study the change (Δ) of LongS after treatment from independent control (non-CAD) and experimental subjects (CAD) with 0.33 control(s) per experimental subject. In a pilot study of 20 CAD and 6 non-CAD patients, the response within each group was normally distributed with an SD of 1.5. The true difference in the CAD and non-CAD means of ΔLongS was 1.1. Therefore, we need to study 60 CAD and 20 non-CAD patients to be able to reject the null hypothesis that the population means for ΔLongS after treatment of the CAD and non-CAD groups are equal with a probability (power) of 0.8, and a type I error probability of 0.05.

Categorical data were compared between patients treated with anakinra and controls by contingency tables. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed variables are given as mean±SD. The Spearman correlation analysis was used to determine bivariate correlations. Data with a non-Gaussian distribution are expressed as median (interquartile range) and were analyzed after transformation into ranks.

ANOVA (general linear model, SPSS 13, SPSS Inc, Chicago, IL) for repeated measurements was applied (1) for the measurement of the examined markers at baseline, 3 hours after placebo, and 3 hours after anakinra, used as a within-subject factor; (2) for the effects of CAD versus non-CAD, with measurements at baseline and 3 hours after treatment, used as a within-subject factor and presence of CAD as a between-subject factor. The F and P values of the interaction between time of measurement of the examined markers and presence of CAD were calculated. The F and P values of the comparison between treatments were calculated. The Greenhouse–Geisser correction was used when the sphericity assumption, as assessed by the Mauchly test, was not met. Post hoc comparisons were performed with Bonferroni correction.

For the determination of interobserver variability, data from the first 20 patients were analyzed by the 2 readers. Intraobserver variability was assessed by repeat (blind) analysis of the same first 20 examinations performed a minimum of 4 weeks after the initial assessment with the corresponding technique. Interobserver and intraobserver variabilities were calculated as the SD of the differences between the first and second measurements and expressed as a percentage of the average value.

Results
Baseline Characteristics of the Study Population
Patient’s clinical characteristics are shown in Table 1. Eighteen (30%) patients with CAD had disease of the left anterior descending artery, 36 (60%) of the circumflex, and 36 (60%) of the right coronary artery. None of the patients had a totally occluded left anterior descending artery. Patients and controls had similar incidence of risk factors (Table 1) with the exception of HDL levels (P<0.05). Compared with controls and patients without CAD, those with CAD were treated to higher percentage with β-blockers and statins (Table 1; P<0.05).

By ANOVA, using post hoc analysis with Bonferroni correction, patients with CAD had 3-fold higher IL-1β levels (P<0.01) but similar disease activity score (P=0.7), erythrocyte sedimentation rate (P=0.9), and C-reactive protein levels (P=0.8) than non-CAD patients (Table 1) in a model including statins and β-blockers. Furthermore, patients with CAD had higher levels of oxidative stress and soluble apoptotic markers as well as lower FMD, CFR, and impaired LV function markers compared with non-CAD patients and controls after adjustment for statins and β-blockers (Tables 2–4; P with Bonferroni correction <0.05).

Thirty-two (53%) and 18 (30%) patients with CAD had wall motion abnormalities and an EF <45%. No adverse effects of the drug were reported. All patients completed the protocol of the study successfully.

Baseline Interrelations Between Biochemical Markers With 2D Speckle Tracking Parameters and Vascular Function Indices
Association of IL-1 With Oxidative Stress and Apoptosis
In all patients, increasing IL-1β was related with increasing malondialdehyde, nitrotyrosine, and PC (r=0.41, r=0.46, r=0.44; P<0.01), as well as with Fas and Fas ligand (r=0.45, r=0.43; P<0.01).

Association of IL-1 and Oxidative Stress With Vascular and LV Dysfunction
In all patients with RA, elevated IL-1β and nitrotyrosine were related with reduced CFR (r=−0.28, P=0.01; r=−0.23, P=0.04), FMD (r=−0.39 and r=−0.38, respectively; P<0.01), systemic arterial compliance (r=−0.39 and r=−0.40, respectively; P<0.01), and increased vascular resistance (r=0.41 and r=0.39, respectively; P<0.01). In addition, elevated IL-1β and PC were related with decreasing LongS (r=−0.41, P<0.01; r=−0.44, P<0.01) and CircS (r=−0.40, P<0.01; r=−0.420, P<0.01). In patients with CAD, elevated PC, nitrotyrosine, and malondialdehyde were related with decreasing EF (r=0.41, P=0.03; r=0.40, P=0.041; r=0.39, P=0.045).

Association of Impaired Coronary and Aortic Function With LV Dysfunction
Impaired CFR was related with reduced LongS (r=−0.458; P<0.01), LongSR (r=−0.334; P=0.02), CircS (r=−0.344; P=0.03), and CircSR (r=−0.413; P<0.01) in all patients. Systemic arterial compliance was related with FMD (r=0.48; P=0.004) and myocardial deformation indices (LongS [r=−0.45; P=0.007], LongSR [r=−0.51; P=0.002], Tw [r=0.40; P=0.048], Tw velocity [r=0.41; P=0.043]).

Similar
Table 2. Acute Effects of Anakinra on Vascular Markers in Rheumatoid Arthritis Patients With CAD Versus Those Without CAD

<table>
<thead>
<tr>
<th>Vascular Marker</th>
<th>CAD (n=60)</th>
<th>Non-CAD (n=20)</th>
<th>CAD</th>
<th>No CAD (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 h After Placebo</td>
<td>3 h After Anakinra</td>
<td>Δ (%)</td>
</tr>
<tr>
<td>VTId rest, cm</td>
<td>11.3±2.7†</td>
<td>11.5±2.6‡</td>
<td>11.5±2.9</td>
<td>9.2±1.4</td>
</tr>
<tr>
<td>VTId hyperemia, cm§</td>
<td>23.8±7.6</td>
<td>23.7±7.4</td>
<td>32.9±10.2</td>
<td></td>
</tr>
<tr>
<td>CFR-VTId§</td>
<td>2.1±0.4¶</td>
<td>2.1±0.4</td>
<td>2.8±1.0</td>
<td></td>
</tr>
<tr>
<td>VTTotal rest, cm</td>
<td>14.8±3.5¶</td>
<td>14.6±4.0</td>
<td>14.9±3.8</td>
<td>12.3±1.7</td>
</tr>
<tr>
<td>VTTotal hyperemia, cm§</td>
<td>30.9±9.8</td>
<td>30.9±9.6</td>
<td>42.7±11.2</td>
<td></td>
</tr>
<tr>
<td>FMD, %§</td>
<td>4.2±1.5¶</td>
<td>4.3±2.3</td>
<td>4.7±2.4</td>
<td></td>
</tr>
<tr>
<td>Systemic arterial compliance, mL·mm·Hg⁻¹·m⁻²§</td>
<td>1130.4±312¶</td>
<td>1138.3±332</td>
<td>1012.2±295</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>129±14</td>
<td>128±12</td>
<td>131±25</td>
<td>127±20</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82±11‡</td>
<td>80±11</td>
<td>83±12</td>
<td>79±12</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±6</td>
<td>68±7</td>
<td>70±6</td>
<td>75±11</td>
</tr>
</tbody>
</table>

Δ% indicates percent difference between baseline and 3 h after anakinra; brachial artery, brachial artery diameter; CAD, coronary artery disease; CFR, coronary flow reserve; DBP, diastolic blood pressure; FMD, flow-mediated dilation of the brachial artery; SBP, systolic blood pressure; VTId, velocity time integral of the diastolic component of coronary flow; and VTTotal, velocity time integral of the overall Doppler waveform of coronary flow.

By ANOVA using post hoc analysis with Bonferroni correction, we obtained the following P value: *P <0.05 for comparisons in baseline measurements for vascular markers in CAD vs non-CAD patients.

†P<0.05 for comparisons of the % difference (Δ) of the measured markers between baseline and 3 h after anakinra in CAD vs non-CAD.

§By ANOVA, there was a significant effect of the type of patients (CAD vs non-CAD) on the changes of CFR-VTId, CFR-VTItotal, FMD, systemic arterial compliance, and resistance between baseline and 3 hours post-anakinra for vascular markers in patients with CAD.

||P<0.05 for change between baseline and 3 h after anakinra for vascular markers in CAD or non-CAD patients.

By ANOVA using post hoc analysis with Bonferroni correction, we obtained the following P value: †P <0.05 for comparisons between controls and baseline measurements for vascular markers in non-CAD patients.

associations were observed among systemic vascular resistance, FMD, and myocardial deformation markers (P<0.05, data not shown).

**Association of Impaired LV Deformation and Twisting With LVEF**

In patients with CAD, decreasing EF values were related with decreasing LongS (r=−0.64; P<0.001), LongSR (r=−0.69; P<0.001), CircS (r=−0.63; P<0.001), CircSR (r=−0.85; P<0.001), Tw (r=0.45; P=0.020), and Tw velocity (r=0.40; P=0.017)

**Effect of Acute Administration of Anakinra**

**Effect of Acute Administration of Anakinra in Vascular Function Markers**

After anakinra treatment, there was a significant improvement in FMD, CFR-VTId, CFR-VTItotal, systemic arterial compliance, and vascular resistance (P for change <0.01; Table 2), reaching values similar to those in controls for CFR, FMD, and arterial compliance (P for comparisons >0.1 using Bonferroni correction; Table 2) in all patients after adjustment for statins and β-blockers. No significant changes were observed after placebo (P>0.1). The improvement in CFR and FMD after anakinra treatment was because of the higher peak coronary flow and peak brachial artery diameter, respectively, in all patients (P for change <0.01; Table 2).

By ANOVA, there was a significant effect of the type of patients (CAD versus non-CAD) on the changes of CFR-VTId, CFR-VTItotal, FMD, systemic arterial compliance, and vascular resistance between baseline and 3 hours post-anakinra after adjustment for statins and β-blockers (F for interaction: F=16.7, F=15.2, F=16.8, F=4.9, and F=7.8, respectively; P<0.01). Thus, compared with baseline, the percent improvement of CFR, FMD, systemic arterial compliance, and resistance was greater in CAD than in non-CAD patients (Table 2; P<0.05).

**Effect of Administration of Anakinra in LV Function Markers**

Three hours after anakinra, there was a significant improvement in tissue Doppler and speckle tracking markers of myocardial deformation and twisting (P for change <0.001; Table 3) in all patients. No significant changes in LV function markers were observed after placebo (P>0.1).
Table 3. Acute Effects of Anakinra on Echocardiographic Markers of Left Ventricular Function in Rheumatoid Arthritis Patients With CAD Versus Those Without CAD

<table>
<thead>
<tr>
<th></th>
<th>CAD (n=60)</th>
<th>Non-CAD (n=20)</th>
<th>CAD</th>
<th>Non CAD</th>
<th>Controls*†‡§ (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 h After Placebo</td>
<td>3 h After Anakinra</td>
<td>Baseline</td>
<td>3 h After Placebo</td>
</tr>
<tr>
<td>2-Dimensional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF, %</td>
<td>49.8±15.1</td>
<td>50.5±15.6</td>
<td>55.6±12.0*¶</td>
<td>65.5±12</td>
<td>65±12</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>124.5±47.9</td>
<td>125.2±48.4</td>
<td>123.5±44.3</td>
<td>90.9±16.9</td>
<td>90±17.1</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>65.6±43.2</td>
<td>66.4±43.4</td>
<td>59.0±33.5</td>
<td>30.2±13.2</td>
<td>30.1±13.4</td>
</tr>
<tr>
<td>SV, mL**</td>
<td>57.2±16.6</td>
<td>57.4±16.8</td>
<td>64.4±16.8</td>
<td>62.8±15.7</td>
<td>62.7±15.9</td>
</tr>
<tr>
<td>Tissue Doppler</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S', cm/s</td>
<td>6.9±1.7</td>
<td>6.9±1.8</td>
<td>8.3±1.5</td>
<td>8.4±2.1</td>
<td>8.3±1.5¶</td>
</tr>
<tr>
<td>E', cm/s</td>
<td>6.8±2.5</td>
<td>6.8±2.4</td>
<td>8.4±2.3</td>
<td>6.8±2.5</td>
<td>6.8±2.4</td>
</tr>
<tr>
<td>E, cm/s</td>
<td>83.4±36.4</td>
<td>83.5±36.7</td>
<td>81.0±39.4</td>
<td>82±34.4</td>
<td>83.1±33.7</td>
</tr>
<tr>
<td>E/E'</td>
<td>14.1±8.9</td>
<td>14.0±8.8</td>
<td>10.7±7.7</td>
<td>10.2±4.0</td>
<td>9.85±3.8#</td>
</tr>
<tr>
<td>Speckle tracking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LongS, %</td>
<td>−14.0±4.3</td>
<td>−14.6±4.2</td>
<td>−18.4±4.5¶</td>
<td>−17.8±3.7</td>
<td>−18.1±3.7</td>
</tr>
<tr>
<td>LongSRS, 1/s</td>
<td>−0.8±0.3</td>
<td>−0.9±0.3</td>
<td>−1.1±0.2¶</td>
<td>−1.0±0.2</td>
<td>−1.0±0.2</td>
</tr>
<tr>
<td>CircS, %</td>
<td>−14.9±4.2</td>
<td>−15.0±4.3</td>
<td>−18.2±4.0¶</td>
<td>−17.3±4.5</td>
<td>−17.5±4.5</td>
</tr>
<tr>
<td>CircSRS, 1/s</td>
<td>−0.9±0.3</td>
<td>−0.9±0.3</td>
<td>−1.1±0.3¶</td>
<td>−1.1±0.2</td>
<td>−1.1±0.2</td>
</tr>
<tr>
<td>Tw, degrees</td>
<td>12.9±5.0</td>
<td>13.2±4.8</td>
<td>16.7±5.0¶</td>
<td>17±4.0</td>
<td>17±4.8</td>
</tr>
<tr>
<td>TwVel, degrees/s</td>
<td>89.5±28.8</td>
<td>89.2±28.5</td>
<td>105.6±28.8</td>
<td>100.5±28.8</td>
<td>100.2±28.5</td>
</tr>
<tr>
<td>UnTwVel, degrees/s</td>
<td>−84.3±35.2</td>
<td>−84.6±35.8</td>
<td>−103.6±48.6¶</td>
<td>−100.3±35.2</td>
<td>−100.6±35.8</td>
</tr>
</tbody>
</table>

Δ% indicates percent difference between baseline and 3 h after anakinra; CAD, coronary artery disease; CircS, circumferential strain; CircSR, circumferential strain; EDV, left ventricular end-diastolic volume; EF, ejection fraction; ESV, left ventricular end-systolic volume; LongS, left ventricular global longitudinal strain; LongSR, left ventricular global longitudinal strain rate; Tw, peak twisting; TwVel, peak twisting velocity; and UnTwVel, untwisting velocity.

P<0.1 for change between baseline and placebo for both CAD and non-CAD patients.

By ANOVA using post hoc analysis with Bonferroni correction we obtained the following P-value:

*P<0.05 for comparisons between controls and baseline measurements of all echocardiography markers in CAD patients.
†P<0.05 for comparisons between controls and baseline measurements for all tissue Doppler and speckle tracking markers in non-CAD patients.
‡P<0.05 for comparisons between controls and 3 h after anakinra measurements of all echocardiography markers in CAD patients.
§P<0.05 for comparisons between controls and 3 h after anakinra measurements for all speckle tracking markers in non-CAD patients.
¶P<0.05 for comparisons in baseline measurements for CAD vs non-CAD patients for all examined echocardiography.
#P<0.05 for change between baseline and 3 h after anakinra for both CAD and non-CAD patients.

**By ANOVA, there was a significant effect of the type of patients (CAD vs non-CAD) on P-value for interaction <0.01.

By ANOVA, there was a significant effect of the type of patients (CAD versus non-CAD) on the changes of (1) S', E', E/E', and E/A' (F for interaction: F=4.3, P<0.04; F=6.3, P=0.016; F=6.2, P=0.019; and F=4.8, P=0.03, respectively); (2) LongS, LongSR, CircS, CircSR (F for interaction: F=14.1, P<0.01; F=15.1 P<0.01; F=4.3, P=0.04; and F=4.2, P=0.04, respectively); (3) Tw, Tw velocity, and UnTw velocity (F for interaction: F=15.3, F=14.2, and F=14.1, respectively; P<0.01); and (4) end-systolic volume, SV, and EF (F for interaction: F=20.3, F=4.9, and F=20.4, respectively; P<0.01)

Table 4. Acute Effects of Anakinra on Regional Deformation Parameters of Left Ventricular function in Rheumatoid Arthritis Patients With Coronary Artery Disease and Wall Notion Abnormalities (n=32)

<table>
<thead>
<tr>
<th>Myocardial Segments</th>
<th>Baseline</th>
<th>3 h After Placebo</th>
<th>3 h After Anakinra</th>
<th>Δ (%)</th>
<th>Baseline</th>
<th>3 h After Placebo</th>
<th>3 h After Anakinra</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normokinetic (n=272)</td>
<td>−16.0±3.2</td>
<td>−15.9±3.1</td>
<td>−21.1±3.4*</td>
<td>33±5</td>
<td>−0.8±0.3</td>
<td>−0.8±0.4</td>
<td>−1.1±0.2*</td>
<td>32±3</td>
</tr>
<tr>
<td>Hypokinetic (n=167)</td>
<td>−12.1±3.9</td>
<td>−12.5±4.1</td>
<td>−15.9±4.0*</td>
<td>31±5</td>
<td>−0.7±0.3</td>
<td>−0.7±0.4</td>
<td>−0.9±0.2*</td>
<td>29±3</td>
</tr>
<tr>
<td>Akinetic and dyskinetic (n=73)</td>
<td>−3.2±3.9</td>
<td>−3±4.0</td>
<td>−3.3±4.2</td>
<td>0±4</td>
<td>−0.2±0.4</td>
<td>−0.2±0.3</td>
<td>−0.2±0.3</td>
<td>0±3</td>
</tr>
</tbody>
</table>

Δ% indicates percent difference between baseline and 3 h after anakinra.

By ANOVA for paired comparisons using Bonferroni correction, we obtained the following P-values:

*P<0.001 for comparisons 3 h after anakinra vs baseline in normokinetic and hypokinetic segments separately, P>0.05 for comparisons 3 h after anakinra vs placebo in normokinetic and hypokinetic segments, and P>0.05 for all comparisons in akinetic segments.
between baseline and 3 hours postanakinra after adjustment for statins and β-blockers. Thus, compared with baseline, the percent improvement in EF, SV, end-systolic volume, LV myocardial deformation, and twisting and untwisting markers was greater in CAD than in non-CAD patients (Table 3; P<0.05).

By ANOVA, using post hoc analysis with Bonferroni correction, LV function markers remained impaired in patients with CAD compared with controls after anakinra (P for all comparisons <0.05; Table 3) in a model including statins and β-blockers. Conversely, in non-CAD patients, LV myocardial deformation and twisting markers after anakinra became similar to those in controls, in the same model (P>0.05; Table 3).

In CAD patients with wall motion abnormalities, LongS and LongSR were improved in normokinetic (F=468.1 and F=469.2, respectively; P<0.001) and hypokinetic segments (F=377.7 and F=379.2, respectively; P<0.001), whereas they remained unchanged in akinetic segments (F=0.11; P=0.7; Table 4) after anakinra.

In patients with CAD, the percent increase of EF after anakinra was related with the percent increase of LongS (r=0.53; P<0.001), LongSR (r=0.397; P=0.045), Tw (r=0.39; P=0.045), Tw velocity (r=0.456; P=0.039), and UnTw velocity (r=0.40; P=0.043).

LV end-diastolic volume and E wave of transmitral flow remained unchanged between baseline and 3 hours after anakinra (Tables 2 and 3; P>0.1), suggesting that preload remained similar throughout the study.

### Table 5. Acute Effects of Anakinra on Biomarkers in Rheumatoid Arthritis Patients With CAD Versus Those Without CAD

<table>
<thead>
<tr>
<th></th>
<th>CAD Patients (n=60)</th>
<th>Non-CAD (n=20)</th>
<th>CAD</th>
<th>Non CAD</th>
<th>Controls* (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline†</td>
<td>3 h After Placebo</td>
<td>3 h After Anakinra</td>
<td>Baseline</td>
<td>3 h After Placebo</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>192.0±59.2</td>
<td>189.9±53</td>
<td>191.6±59</td>
<td>212.1±46</td>
<td>209.9±40</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>120.8±37.5</td>
<td>119.7±35.4</td>
<td>121.5±38</td>
<td>132.1±40</td>
<td>130.9±38</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>47.4±14.7</td>
<td>51.1±15</td>
<td>47.2±14.9</td>
<td>66.1±18</td>
<td>66.8±19</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>136.0±94.8</td>
<td>141.7±96</td>
<td>136.6±95</td>
<td>122.2±46</td>
<td>127.9±46</td>
</tr>
<tr>
<td>Fas, pg/mL‡</td>
<td>535</td>
<td>517</td>
<td>334§</td>
<td>481</td>
<td>485</td>
</tr>
<tr>
<td>FasL, pg/mL‡</td>
<td>476</td>
<td>477</td>
<td>307§</td>
<td>289</td>
<td>285</td>
</tr>
<tr>
<td>MDA, nM/L‡</td>
<td>2.85</td>
<td>2.84</td>
<td>1.85§</td>
<td>2.2</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>(1.95–3.8)</td>
<td>(1.90–3.56)</td>
<td>(1.26–2.1)</td>
<td>(1.5–3.3)</td>
<td>(1.3–3.7)</td>
</tr>
<tr>
<td>Nitrotyrosine, nM/L‡</td>
<td>866</td>
<td>869</td>
<td>450§</td>
<td>787</td>
<td>707</td>
</tr>
<tr>
<td></td>
<td>(55–4625)</td>
<td>(55–4620)</td>
<td>(33–1805)</td>
<td>(92–903)</td>
<td>(5.8–935)</td>
</tr>
<tr>
<td>Protein carbonyl, nmol/mg protein‡</td>
<td>0.141</td>
<td>0.142</td>
<td>0.091§</td>
<td>0.111</td>
<td>0.110</td>
</tr>
</tbody>
</table>

*Δ% indicates percent difference between baseline and 3 h after anakinra, CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDA, malondialdehyde; and MDA, malondialdehyde.

†P<0.01 for change between baseline and placebo for both CAD and non-CAD patients.

‡P<0.05 for comparisons between controls and baseline measurements for apoptotic and oxidative stress markers in CAD and non-CAD patients.

§P<0.05 for comparisons in baseline measurements for apoptotic and oxidative stress markers in CAD versus non-CAD patients.

<table>
<thead>
<tr>
<th></th>
<th>Controls*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline†</td>
</tr>
<tr>
<td></td>
<td>3 h After Placebo</td>
</tr>
<tr>
<td></td>
<td>3 h After Anakinra</td>
</tr>
<tr>
<td></td>
<td>Baseline†</td>
</tr>
<tr>
<td></td>
<td>3 h After Placebo</td>
</tr>
<tr>
<td></td>
<td>3 h After Anakinra</td>
</tr>
<tr>
<td></td>
<td>Δ (%)</td>
</tr>
<tr>
<td></td>
<td>Δ (%)</td>
</tr>
<tr>
<td></td>
<td>Controls†</td>
</tr>
</tbody>
</table>

### Effect of Acute Administration of Anakinra in Oxidative Stress and Apoptotic Markers

Compared with baseline, there was a significant decrease in the serum levels of nitrotyrosine, malondialdehyde, PC, Fas, and Fas ligand after anakinra (Table 5; P<0.01) in all patients. No significant changes in biochemical markers were observed after placebo (P for change >0.1).

By ANOVA, there was a significant effect of the type of patients (CAD versus non-CAD) on the changes of nitrotyrosine, malondialdehyde, and PC (F for interaction: F=7.8, F=7.6, P<0.01 and F=9.8, P<0.01, respectively) as well as on changes of Fas and Fas ligand (F for interaction: F=7.9 and F=7.5, respectively; P<0.01) between baseline and 3 hours postanakinra after adjustment for statins and β-blockers. Thus, compared with baseline, the percent decrease of nitrotyrosine, malondialdehyde, and PC as well as of Fas and Fas ligand was greater in CAD than in non-CAD patients (Table 2; P<0.05).

Baseline and postplacebo values of all the examined echocardiography and biochemical markers were similar (Table 5; P>0.1). This finding suggests that any potential carryover effect of anakinra during the acute administration of the drug was minimal.

### Association of Baseline IL-1 Levels With the Response to Anakinra Treatment

In patients with CAD, there was an association between baseline IL-1β levels and increasing change in FMD, LongS, LongSR peak Tw, Tw, and UnTw velocities after anakinra (r=0.30, r=0.32, r=0.33, r=0.48, r=0.47, and r=0.48, respectively; P<0.01; Figure).
Discussion

In this acute, double-blind, crossover, placebo-controlled study of patients with RA, we found that treatment with a recombinant IL-1 receptor antagonist (anakinra) causes a greater improvement in LV myocardial deformation, twisting, and untwisting than placebo. This improvement was greater in patients with CAD compared with those without and resulted in a concomitant improvement of the LVEF in patients with CAD. These beneficial effects were linked with a greater reduction of oxidative stress by anakinra treatment in patients with CAD compared with those without. In addition, the greater improvement in CFR, arterial compliance, and vascular resistance by anakinra in CAD compared with non-CAD patients may also explain the increased benefit of IL-1 inhibition on LV function in patients with CAD.

Baseline Differences Between RA Patients With and Without CAD

Local release and increased circulating levels of IL-1 are observed in both CAD and RA and are linked with increased oxidative stress and endothelial and myocardial damage. In the present study, we have shown that circulating IL-1β levels in RA patients with CAD were 3-fold higher compared with those without CAD and similar RA disease activity. This finding suggests that the inflammatory and atherogenic processes characterizing RA and CAD have an additive effect on IL-1 production. Enhanced IL-1 activity is related to increased oxidative stress and specifically with protein oxidation as assessed by PC. In the present study, circulating IL-1β was related with all measured oxidative stress markers in all patients. More importantly, as with IL-β levels, patients with CAD had higher levels of oxidative stress and apoptosis markers compared with non-CAD patients at baseline. This finding suggests that the higher IL-1β activity may have also resulted in greater oxidative stress and apoptosis in CAD than in non-CAD patients.

In the present study, the patients with CAD had lower FMD and CFR compared with non-CAD patients and controls. At baseline, both increased IL-1β levels and oxidative stress were associated with reduced FMD and CFR. IL-1 induces NADPH oxidase expression, leading to reactive oxygen species production which in turn reduces endothelial function and favors artery vasoconstriction. Therefore, we may speculate that a larger IL-1–driven oxidative burden may have contributed to the lower FMD and CFR observed in our patients with CAD compared with those without CAD.

In our study, patients with CAD had lower LV end-systolic volume, LV deformation, and twisting markers compared with non-CAD patients and controls. At baseline, both increased circulating IL-1β and oxidative stress markers were associated with reduced LV myocardial deformation and twisting–untwisting, as well as with reduced EF in our patients with CAD. IL-1 activity may cause reversible myocardial dysfunction through (1) a direct detrimental effect on cardiac mitochondria as well as on mitochondrial respiratory chain, and (2) reduction of endothelial nitric oxide synthase and production of inducible nitric oxide synthase, intracellular reactive oxygen species, peroxynitrite, and cytokines with a negative inotropic action such as interleukin-6. In patients with CAD, the prepercutaneous intervention levels of IL-1β contributed to prediction of LV end-systolic volume, and postpercutaneous intervention levels of IL-1β determined LV volumes. In addition, the greater reduction of CFR and endothelial nitric oxide synthase, as assessed by FMD, may have also contributed to the greater myocardial dysfunction in the CAD compared with non-CAD patients in our study.

Thus, the 3-fold higher IL-1β levels and the higher oxidative stress in CAD versus non-CAD patients may explain the greater impairment of endothelial and coronary microcirculatory function and may have contributed to the impaired LV myocardial deformation, twisting, and untwisting of the patients with CAD in the present study.

Effects of IL-1 Inhibition on LV Function in CAD Versus Non-CAD

Studies support that lowering IL-1 activity has a rapid beneficial effect on cell function. In particular, the rapid improvement of LV myocardial deformation, twisting, and untwisting observed in the present study may be explained by (1) rapid inhibition of nuclear factor-xB, inducible nitric oxide synthase, and interleukin-6 combined with a concomitant increase in endothelial nitric oxide synthase, as confirmed.

Figure. Association between baseline interleukin-1β (IL-1β) levels and increasing percent change in flow-mediated dilatation (dFMD%; A) and longitudinal strain (dLongS%; B) after anakinra (r=0.30 and r=0.32; P<0.01).
by an improved FMD\textsuperscript{25-27}, (2) reduction of peroxynitrate, lipid, and protein peroxidation, as assessed by reduction of nitrotyrosine, malondialdehyde, and PC, respectively\textsuperscript{15-17,27}, (3) improved mitochondrial function\textsuperscript{21} after inhibition of IL-1 activity by anakinra; and (4) improved coronary microcirculatory function as assessed by CFR and arterial wall elastic properties as assessed by systemic arterial compliance and resistance. However, this improvement was more evident in the patients with CAD compared with their non-CAD counterparts likely because of the 3-fold higher levels of IL-1\( \beta \) and the 2-fold greater oxidative burden observed in CAD than in non-CAD patients at baseline. In the present study, increased baseline IL-1\( \beta \) blood levels were related with greater improvement in FMD, myocardial deformation, and LV twisting–untwisting markers in patients with CAD. In addition, the reduction of the direct or oxidative stress–mediated action of IL-1 is expected to elicit more benefits on LV function in CAD patients with severe myocardial dysfunction than in patients with a preserved EF and no myocardial ischemia because of the absence of CAD. Thus, inhibition of IL-1 activity offers a greater benefit on vascular and LV function in patients with CAD because it reduces a larger baseline IL-1 activity and oxidative burden on the grounds of a greater impairment of LV function in CAD compared with non-CAD patients.

Anakinra has been shown to reduce experimental myocardial infarction through inhibition of apoptosis and to improve LV volumes after myocardial infarction.\textsuperscript{28} Enhanced intracellular IL-1 receptor antagonist synthesis is found at 3 hours of dial infarction through inhibition of apoptosis and to improve oxidative burden on the grounds of a greater impairment of LV function in CAD compared with non-CAD patients. Anakinra may be a marker for a larger oxidative and inflammatory burden and hence, an increased likelihood to respond to IL-1 inhibition treatment. Furthermore, the acute effects of single dose of anakinra on vascular and LV function of our patients with CAD should be confirmed in larger scale trials.

Conclusions

In the present study, we have shown that IL-1\( \beta \), oxidative stress, and, in particular, protein oxidation are higher in RA patients with CAD compared with those without. Both increased IL-1\( \beta \) and oxidative stress were associated with impaired vascular function as well as with abnormal LV myocardial deformation, twisting, and untwisting. Inhibition of IL-1 activity by anakinra treatment was associated with greater reduction in oxidative stress in parallel with a greater improvement of vascular function, LV myocardial deformation, twisting, and untwisting in patients with CAD compared with those without, resulting in an improved LVEF.

A multicenter secondary prevention trial with canakinumab in patients with prior myocardial infarction is currently ongoing and may validate the effects of IL-1 inhibition in CAD.\textsuperscript{20}

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\textbf{Disclosures}

None.

\textbf{References}


Increased Benefit of Interleukin-1 Inhibition on Vascular Function, Myocardial Deformation, and Twisting in Patients With Coronary Artery Disease and Coexisting Rheumatoid Arthritis

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