

ORIGINAL INVESTIGATIONS

Randomized Trial of Interleukin-6 Receptor Inhibition in Patients With Acute ST-Segment Elevation Myocardial Infarction



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ABSTRACT

BACKGROUND Prompt myocardial revascularization with percutaneous coronary intervention (PCI) reduces infarct size and improves outcomes in patients with ST-segment elevation myocardial infarction (STEMI). However, as much as 50% of the loss of viable myocardium may be attributed to the reperfusion injury and the associated inflammatory response.

OBJECTIVES This study sought to evaluate the effect of the interleukin-6 receptor inhibitor tocilizumab on myocardial salvage in acute STEMI.

METHODS The ASSAIL-MI trial was a randomized, double-blind, placebo-controlled trial conducted at 3 high-volume PCI centers in Norway. Patients admitted with STEMI within 6 h of symptom onset were eligible. Consenting patients were randomized in a 1:1 fashion to promptly receive a single infusion of 280 mg tocilizumab or placebo. The primary endpoint was the myocardial salvage index as measured by magnetic resonance imaging after 3 to 7 days.

RESULTS We randomized 101 patients to tocilizumab and 98 patients to placebo. The myocardial salvage index was larger in the tocilizumab group than in the placebo group (adjusted between-group difference 5.6 [95% confidence interval: 0.2 to 11.3] percentage points, $p = 0.04$). Microvascular obstruction was less extensive in the tocilizumab arm, but there was no significant difference in the final infarct size between the tocilizumab arm and the placebo arm (7.2% vs. 9.1% of myocardial volume, $p = 0.08$). Adverse events were evenly distributed across the treatment groups.

CONCLUSIONS Tocilizumab increased myocardial salvage in patients with acute STEMI. (ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction [ASSAIL-MI]; NCT03004703) (J Am Coll Cardiol 2021;77:1845-55) © 2021 by the American College of Cardiology Foundation.



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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging

CRP = C-reactive protein

IL = interleukin

I/R = ischemia/reperfusion

MI = myocardial infarction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TnT = cardiac troponin T

The mortality and morbidity associated with ST-segment elevation myocardial infarction (STEMI) have fallen in the era of primary percutaneous coronary intervention (PCI) (1); however, the residual morbidity is substantial. A large proportion of patients subsequently develop heart failure, which is associated with an increased risk of death (2). The area at risk, that is, the volume of the myocardium that is rendered ischemic by the coronary occlusion, is the most important determinant of the final infarct size (3), which in turn influences outcomes (4). Another important factor is myocardial salvage; the extent to which the ischemic myocardium recovers after reperfusion (5).

Paradoxically, the restoration of blood flow to the ischemic area may result in further myocardial injury. The pathophysiological mechanisms causing this ischemia/reperfusion (I/R) injury are not fully elucidated, but may involve the generation of reactive oxygen species, intracellular calcium overload, and acidosis (6). The I/R injury may account for as much as 50% of the myocardial damage in myocardial infarction (MI), and inflammatory mechanisms seem to contribute to the I/R injury (6). A dysregulated inflammatory process can increase the final infarct size, induce maladaptive remodeling within the myocardium, and lead to heart failure (7). Targeted therapy against inflammatory pathways that are activated during reperfusion could be a target for reducing the final infarct size and improve prognosis after STEMI. Cardiac magnetic resonance imaging (CMR) can be used to quantify the extent of myocardial ischemia and necrosis and thus to estimate the effect of such intervention.

The inflammatory cytokine interleukin (IL)-6 is an important mediator of the inflammatory process in coronary artery disease, and may also contribute to the I/R injury in MI (8,9). Levels of IL-6 increase

substantially after MI and are associated with poor short-term outcomes (10). Tocilizumab is a recombinant humanized monoclonal antibody that binds to the IL-6 receptor to block its signal transmission. Tocilizumab is approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and giant cell arteritis and protects against cardiovascular events induced by chimeric antigen receptor T-cell therapy (11).

We recently conducted a double-blind, placebo-controlled trial in 117 patients with non-STEMI who presented within 72 h of the onset of chest pain. In this study, a single, intravenous dose of tocilizumab reduced levels of C-reactive protein (CRP), a downstream marker of IL-6, by >50% in the days after the intervention (12). Importantly, tocilizumab also reduced levels of troponin T (TnT) after revascularization, suggesting that tocilizumab reduced the magnitude of the I/R injury. On the other hand, the potential for myocardial salvage is larger in transmural infarctions. We therefore designed the ASSAIL-MI (Assessing the effect of Anti-IL-6 treatment in Myocardial Infarction) trial to test the hypothesis that prompt administration of tocilizumab would increase the myocardial salvage index in patients presenting with acute STEMI (13).

SEE PAGE 1856

METHODS

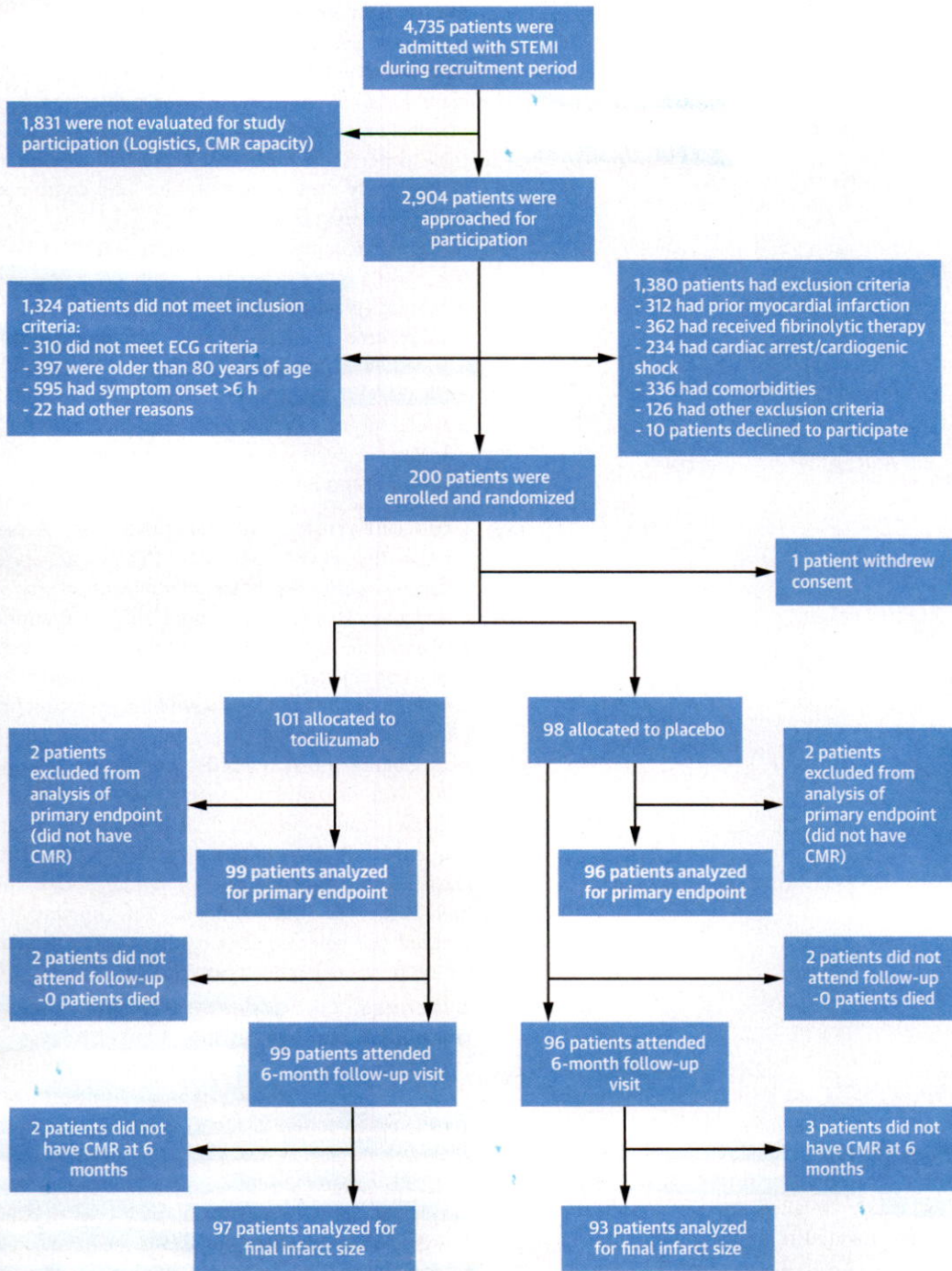
TRIAL DESIGN AND PARTICIPANTS. This phase II, parallel arm, double-blind, randomized, placebo-controlled trial was conducted at 3 high-volume PCI centers in Norway (Oslo University Hospital Rikshospitalet, Oslo University Hospital Ullevål, and St. Olav's Hospital, Trondheim). Patients aged between 18 and 80 years were eligible for participation if presenting with chest pain within 6 h of symptom onset and ST-segment elevation in 2 contiguous electrocardiogram leads consistent with acute transmural MI (14). Key exclusion criteria

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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FIGURE 1 Screening, Randomization, and Follow-Up



Flow chart illustrating patient selection, randomization, and follow-up. CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; STEMI = ST-segment elevation myocardial infarction.

were previous MI; left bundle branch block; chronic infection, or chronic autoimmune or inflammatory disease; uncontrolled bowel disease; resuscitated cardiac arrest; fibrinolytic therapy within the last 72 h; a history of ongoing infectious or immunologic disease; major surgery within the past 8 weeks; or treatment with

TABLE 1 Baseline Characteristics

	Tocilizumab (n = 101)	Placebo (n = 98)
Demographics		
Age, yrs	62 ± 10	60 ± 9
Men	80 (79)	87 (89)
Body mass index, kg/m ²	27.1 ± 4.5	27.5 ± 4.3
White	99 (98)	94 (96)
Smoking status		
Never smokers	38 (38)	36 (37)
Previous smokers	33 (33)	24 (24)
Current smokers	30 (30)	38 (39)
Prior conditions		
Angina pectoris	1 (1)	1 (1)
Cerebrovascular disease	4 (4)	2 (2)
Other vascular disease	1 (1)	3 (3)
Diabetes mellitus	8 (8)	6 (6)
Hypertension	33 (33)	30 (31)
Treatment		
ACE inhibitor or ARB	22 (22)	25 (26)
Aldosterone antagonist	1 (1)	0 (0)
Oral anticoagulants	5 (5)	2 (2)
Platelet inhibitor	12 (12)	5 (5)
Beta-blocker	8 (8)	3 (3)
Calcium antagonist	13 (13)	10 (10)
Diuretic	8 (8)	8 (8)
Statin	19 (19)	9 (9)
Up-front DAPT	101 (100)	98 (100)
Clinical characteristics		
Blood pressure at admission, mm Hg		
Systolic	131 ± 23	132 ± 22
Diastolic	81 ± 17	84 ± 16
Heart rate at admission, beats/min	71 ± 15	73 ± 18
Time from symptom onset to arrival at PCI center, min	151 ± 71	149 ± 72
Door-to-balloon time, min	23 ± 10	23 ± 11
Killip class		
I	96 (95)	95 (97)
II	4 (4)	3 (3)
III	0 (0)	0 (0)
IV	1 (1)	0 (0)
GRACE risk score	140 ± 25	135 ± 21

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immunosuppressants other than low-dose steroids (equivalent to a systemic exposure to 5 mg prednisone per day). Detailed inclusion and exclusion criteria are provided in Supplemental Table 1.

ETHICAL CONSIDERATIONS. The trial protocol was approved by the regional ethics committee (REK Sør-Øst 2016/1223), and all participants provided written informed consent. An independent Data and Safety Monitoring Board oversaw the safety of the trial. The trial was conducted in compliance with the declaration of Helsinki and with the rules outlined in the guidelines for Good Clinical Practice. Before

commencing enrollment, we registered the trial with ClinicalTrials.gov, number NCT03004703.

STUDY SETTING AND INTERVENTION. Patient eligibility was assessed after admission, *en route* to the catheterization laboratory. The study procedures were designed not to delay revascularization. A brief physical examination was performed on the operating table as per usual routine. Oral consent was obtained before study drug administration, and confirmed in writing the next day.

The participants were randomized in a 1:1 fashion to receive a single intravenous dose of tocilizumab or matching placebo during PCI. Tocilizumab was administered at a fixed dose of 280 mg dissolved in 100 ml NaCl 0.9%. The intravenous infusion was administered over 1 h, as recommended by the drug manufacturer (1.67 ml/min). Patients allocated to placebo received an identical-looking intravenous infusion of 100 ml NaCl 0.9%.

RANDOMIZATION AND MASKING. The Research Support Unit at Oslo University Hospital generated a balanced, permuted block randomization list with varying block sizes. The randomization was stratified by center and by whether the time from symptom onset was shorter or longer than 3 h. Patients, study personnel, and caretakers were blinded to treatment allocation. Unblinded personnel pre-prepared identical-looking infusion bottles containing the active study drug or placebo. For treatment allocation, the blinded study personnel selected the next-in-sequence infusion container, according to whether the time from symptom onset was <3 h or 3 h or more, and registered the randomization number. This method was selected for expedient study drug allocation in the emergency care setting.

OUTCOMES. The primary endpoint was the myocardial salvage index (%) defined as:

$$\left(\frac{\text{area at risk} - \text{infarct size}}{\text{area at risk}} \right) \times 100$$

measured by CMR 3 to 7 days after the intervention. The area at risk is the myocardial volume that is rendered ischemic by the coronary occlusion, whereas the infarct size is the volume of necrotic myocardium. Pre-specified secondary endpoints included: 1) final infarct size (in % of left ventricular mass) as measured by CMR 6 months after the intervention; 2) microvascular obstruction; 3) the area under the curve for TnT; 4) CRP during index hospitalization; 5) N-terminal pro-B-type natriuretic peptide (NT-proBNP); 6) baseline-adjusted left ventricular end-diastolic volume at 6 months; and 7) safety and tolerability. For details, see Supplemental Table 2.

SAMPLE SIZE. We did not perform a sample size analysis based on assumptions about the data that we expected to obtain in the ASSAIL-MI trial, but relied on sample size calculations from the CHILL-MI (Efficacy of Endovascular Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction) and MITOCARE (Treatment of reperfusion injury using a mitochondrial targeted approach: towards a better understanding of the disease) trials as described by Engblom et al. (15). We assumed that our patients would not differ substantially from the patients enrolled in these trials, in whom the mean \pm SD for the myocardial salvage index was 54.0% \pm 19.4%, and the mean \pm SD of the infarct size was 17.4% \pm 10.5% of left ventricular mass.

With a SD of 20% and 2 \times 100 patients, our trial has 90% power to statistically detect an underlying treatment effect on the myocardial salvage index of 9.2 percentage points. Studies have shown that a treatment effect of this magnitude is associated with improved survival and a reduction in clinical events (16).

FOLLOW-UP. The patients were hospitalized for a minimum of 3 days after PCI. Blood samples for assessments of efficacy and safety were drawn before administration of the investigational medicinal product, and again after approximately 8, 16, 24, and 72 to 168 h after admission, as well as after 3 and 6 months. CMR was performed at 3 to 7 days, and at 6 months.

ASSESSMENTS. CMR was performed on 1.5-T systems (Siemens Avanto, Philips Ingenia). A gadolinium contrast agent was administered (0.15 mmol/kg gadobutrol or 0.22 mmol/kg Gd-DOTA), and after 5 min, we acquired a stack of short-axis images of the left ventricle using a retrospectively electrocardiogram-gated, steady-state free precession cine sequence with minimum echo and repetition times. The slice thickness was 8 mm, there were no interslice gaps, the spatial resolution was approximately 1.5 \times 1.5 mm, and the temporal resolution 30 to 35 ms. After 15 min, corresponding late enhancement images were acquired in the same image positions (inversion recovery snapshot fast low-angle shot [FLASH]). The same protocol was used at the 6-month examination.

All CMR images were analyzed by a core laboratory at the Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway, using the Segment software (Medviso, Lund, Sweden) (17). Left ventricular mass, volumes, and ejection fraction were analyzed according to recommendations. The area at risk was

TABLE 1 Continued

	Tocilizumab (n = 101)	Placebo (n = 98)
Infarct location		
Left anterior descending branch	38 (38)	36 (37)
Circumflex or marginal	11 (11)	13 (13)
Right coronary artery	47 (47)	46 (49)
Other	5 (5)	3 (3)
Laboratory values		
Hemoglobin, g/l	143 \pm 13	144 \pm 12
Platelet count, 10 ⁹ /l	253 \pm 59	260 \pm 62
Total white blood cell count, 10 ⁹ /l	11.6 \pm 3.4	11.6 \pm 3.4
Aspartate transaminase, U/l	28 (22-37)	30 (24-37)
Troponin T, ng/l	44 (22-163)	49 (28-95)
CK-MB, μ g/l	5.0 (2.6-14.0)	5.3 (3.0-10.0)
NT-proBNP, ng/l	79 (50-178)	63 (50-146)
Creatinine, mmol/l	74 \pm 17	78 \pm 20
Glucose, mmol/l	9 \pm 3	9 \pm 3
HbA1c, mmol/mol	37 (34-41)	37 (34-40)
Total cholesterol, mmol/l	5.3 \pm 1.2	5.2 \pm 1.0
HDL cholesterol, mmol/l	1.2 (0.9-1.3)	1.1 (0.9-1.3)
LDL cholesterol, mmol/l	3.7 \pm 1.1	3.7 \pm 0.9
C-reactive protein, mg/l	2.4 (0.9-5.0)	2.9 (1.4-5.0)
Albumin, g/l	42 \pm 3	42 \pm 3

Values are mean \pm SD, n (%), or median (interquartile range). Baseline characteristics stratified by treatment allocation.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CK-MB = creatine kinase myocardial band; DAPT = dual anti-platelet therapy; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

quantified using the short-axis early contrast-enhanced images as previously described (17), with end-diastolic and end-systolic values averaged. Infarct size was quantified using the expectation maximization, weighted intensity, a priori information method with manual correction. This method has been experimentally and clinically validated, and agrees well with expert delineation (18).

High-sensitivity CRP and NT-proBNP were analyzed on a MODULAR platform (Roche Diagnostics, Basel, Switzerland), and high-sensitivity TnT was measured by electrochemiluminescence immunoassay (Elecsys 2010 analyzer, Roche Diagnostics). Safety samples were analyzed consecutively using routine laboratory methods. In addition, safety was assessed through comprehensive patient interviews, review of patient records, physical examination, and blood samples for safety, as well as echocardiography and CMR.

STATISTICS. Analyses were performed on an intention-to-treat basis. Continuous data are summarized by the mean \pm SD or median (interquartile range) if distributions were skewed. Categorical data

are reported as numbers and percentages. Normally distributed endpoints, including the primary endpoint, were analyzed using parametric methods. The analysis of the primary endpoint was adjusted for the time from symptom onset, the pre-determined stratification variable. The baseline-adjusted between-group difference in left ventricular end-diastolic volume was calculated by analysis of covariance with treatment as a fixed effect and the baseline volume as a covariate. The areas under the curve of TnT and CRP were calculated by the quadratic method. The between-group differences in TnT, CRP, microvascular obstruction, and final infarct size were assessed by Mann-Whitney *U* tests due to skewed distributions. There were no imputations for missing data.

We did not perform interim outcome analyses. We assessed the consistency of the treatment effect on the primary endpoint among 6 pre-specified subgroups that were analyzed individually and then in a multivariable model. The following a priori subgroup analyses were planned: age younger than versus older than 60 years, duration from symptom onset to study drug infusion less than versus at least 3 h, female versus male sex, area at risk above versus below median, and the areas under the curve for TnT and CRP above versus below median. Safety analyses included tabulation of type and frequency of all adverse events and severe adverse events. All statistical analyses were performed in SPSS version 25 (IBM Corp., Armonk, New York). Two-sided probability values were considered significant at $p < 0.05$. The *p* values and 95% confidence intervals presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible.

RESULTS

Between March 16, 2017, and February 13, 2020, we enrolled 200 patients. One patient gave oral consent, but later refused to participate in the trial and would not allow the use of his or her data. In 4 patients, the CMR at 3 to 7 days was not performed. Therefore, 195 patients had data available for the analysis of the primary endpoint: 96 patients in the placebo group and 99 in the tocilizumab group (Figure 1). Baseline data were well balanced between the study arms (Table 1).

Coronary angiography was performed in all patients. The door-to-balloon time was 23 ± 10 min. All patients underwent primary PCI except for 8 patients who were deemed not to have MI, 5 patients in the tocilizumab arm and 3 allocated to placebo. Optimal

medical therapy was provided according to prevailing guidelines. No patients received urgent coronary artery bypass grafting. The primary endpoint CMR was performed 5.0 ± 1.3 days after inclusion in the tocilizumab arm and 5.0 ± 1.3 days after inclusion in the placebo arm ($p = 1.00$). A total of 195 patients attended the 6-month follow-up-visit (99 in the tocilizumab arm and 96 in the placebo arm). Vital status was known for all participants. No patients died during 6 months of follow-up.

Table 2 shows the results for the primary and key secondary endpoints. The adjusted myocardial salvage index was higher in the tocilizumab arm than in the placebo arm ($69 \pm 19\%$ vs. $64 \pm 21\%$). The between-group difference was 5.6 percentage points (95% confidence interval: 0.2 to 11.3; $p = 0.04$) (Figure 2). The median final infarct size measured 6 months after the intervention was 21% lower in the tocilizumab arm, but this difference was not statistically significant ($p = 0.08$). The area under the curve of TnT during hospitalization was numerically lower in patients allocated to tocilizumab, but once again, the between-group difference was not statistically significant ($p = 0.13$). On the other hand, the extent of microvascular obstruction was significantly less in the tocilizumab arm than in the placebo arm ($p = 0.03$). The area under the curve of CRP during hospitalization was substantially lower in the tocilizumab group than in the placebo group ($p < 0.001$). Finally, there were no between-group differences in the baseline-adjusted left ventricular volume ($p = 0.54$) or the plasma concentration of NT-proBNP at 6 months ($p = 0.25$). Comprehensive results of the CMR examinations are provided in Table 3 and the laboratory analyses in Supplemental Table 3.

The primary outcome in the 6 pre-specified subgroups is shown in Figure 3. There was heterogeneity of the treatment effect regarding the time from symptom onset. Notably, the positive effect of tocilizumab on the primary endpoint seemed to be limited to patients presenting >3 h after symptom onset. Men appeared to benefit more than women from treatment with tocilizumab, but the interaction between sex and treatment was of borderline statistical significance ($p = 0.053$).

We observed 77 minor adverse events in the tocilizumab group and 85 events in the placebo arm during 6 months' follow-up. Most of the events were mild and deemed not to be associated with the study drug. Serious adverse events are tabulated in Table 4. There were 19 serious adverse events in patients allocated to tocilizumab and 15 serious adverse events in patients allocated to placebo ($p = 0.57$). Notably, there were no myocardial ruptures. There

TABLE 2 Primary and Secondary Outcomes

	Tocilizumab		Placebo		Between-Group Difference (95% CI)	p Value*
Myocardial salvage index, %	69.3 ± 19.3	99	63.6 ± 20.8	96	5.6 (0.2 to 11.3)	0.04
Final infarct size at 6 months (% of left ventricular mass)	7.2 (2.6 to 11.8)	97	9.1 (2.9 to 16.3)	93	-	0.08
Extent of microvascular obstruction (% of left ventricular volume)	0 (0 to 14)	99	4 (0 to 18)	96	-	0.03
Troponin T AUC, ng/l/h	1,614 (860 to 3,515)	101	2,357 (97 to 4,127)	98	-	0.13
C-reactive protein AUC, mg/l/h	1.9 (0.9 to 4.9)	101	8.6 (5.0 to 17.9)	98	-	<0.001
Baseline-adjusted LVEDV at 6 months, ml	157 (151 to 166)	97	160 (153 to 166)	93	3 (-6 to 11)	0.54
NT-proBNP at 6 months, ng/l*	79 (50 to 187)	98	63 (50 to 148)	97	32 (-84 to 149)	0.25

Values are mean ± SD, n, or median (interquartile range), unless otherwise indicated. Primary and secondary endpoints. *We did not adjust for multiple testing, and all p values are nominal only.

AUC = area under the curve; CI = confidence interval; LVEDV = left ventricular end-diastolic volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

were 3 infections requiring prolongation of the index hospitalization or renewed hospitalization in the tocilizumab arm and 2 such infections in the placebo arm. No patients died or developed heart failure during follow-up.

There were minor differences in biochemical variables between the 2 treatment groups that could potentially reflect side effects of tocilizumab (Supplemental Table 3). First, there was an early decrease in neutrophils and monocytes in the tocilizumab arm. Second, low-density lipoprotein and triglycerides increased in the tocilizumab arm compared with the placebo arm. Finally, we observed a very modest increase in liver enzymes in the tocilizumab group. Importantly, at 3 and 6 months, there were no between-group differences in these parameters.

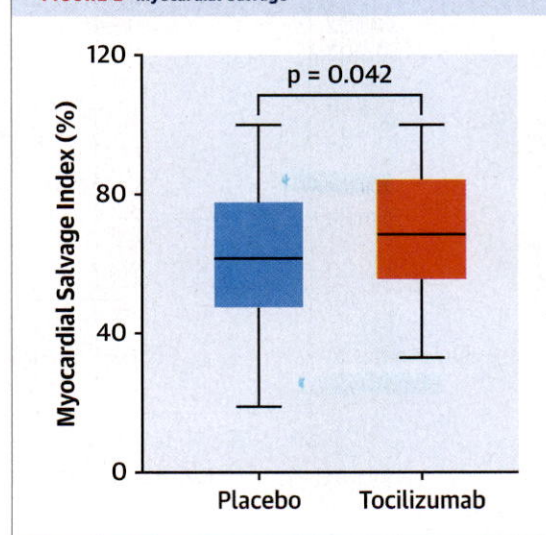
DISCUSSION

This randomized trial showed that prompt, intravenous treatment with the IL-6 inhibitor tocilizumab may improve myocardial salvage in patients presenting with acute STEMI (Central Illustration). This effect seemed to be limited to patients with symptom onset >3 h before PCI. The extent of microvascular obstruction was less in the tocilizumab arm than in the placebo arm.

Inflammation seems to be involved in all stages of atherosclerotic disease, from the development of the initial lesion to plaque progression, rupture, and erosion, and appears to contribute to the I/R injury after revascularization. The Canakinumab Antiinflammatory Thrombosis Outcomes Study (19), the Colchicine Cardiovascular Outcomes Trial (20), and the Low-dose colchicine for secondary prevention of cardiovascular disease trial (21) showed that anti-inflammatory treatment can reduce cardiovascular

events in patients with coronary artery disease. However, the effect of anti-inflammatory treatment on the I/R injury has been explored to a limited degree only (22). In a small randomized trial, methotrexate did not reduce infarct size and seemed to impair left ventricular function after STEMI (23). Treatment with the IL-1 receptor antagonist anakinra was recently shown to attenuate inflammation in the wake of STEMI. Although there was no difference in left ventricular volume or ejection fraction between the anakinra arm and the placebo arm, the incidence of death or new-onset heart failure or of death and

FIGURE 2 Myocardial Salvage



Bar chart showing myocardial salvage in patients treated with tocilizumab and patients treated with placebo.

TABLE 3 Cardiac Magnetic Resonance Imaging Data

	3-7 Days After Randomization			6 Months After Randomization		
	Tocilizumab	Placebo	p Value for Difference	Tocilizumab	Placebo	p Value for Difference*
LVEDV, ml	149 ± 39	157 ± 40	0.17	153 ± 45	163 ± 47	0.12
LVESV, ml	80 ± 22	81 ± 18	0.88	85 ± 222	88 ± 19	0.46
LVEF, %	55 ± 10	53 ± 10	0.18	56 ± 11	55 ± 10	0.53
Area at risk, g	46 ± 24	51 ± 30	0.16	N/A	N/A	
LV mass, g	131 ± 29	135 ± 34	0.46	118 ± 33	124 ± 32	0.22
Infarct size, g	12.6 (6.9-23.6)	15.0 (6.8-31.2)	0.14	7.9 (2.7-15.5)	11.7 (3.3-21.9)	0.09
MVO	35 (35)	49 (51)	0.02	10 (10)	11 (12)	0.46

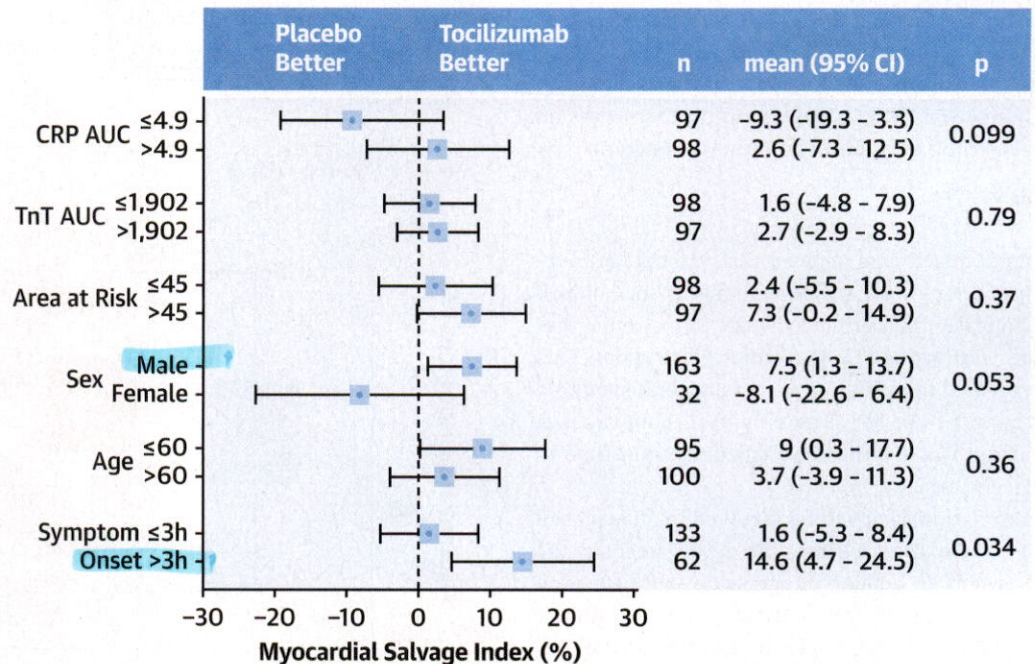
Values are mean ± SD or median (interquartile range) depending on distribution, or n (%). *p values are nominal.
LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MVO = microvascular obstruction.

hospitalization for heart failure was lower in patients treated with anakinra (24). Similar results were observed in a pooled analysis of the pilot trials (25). On the other hand, we recently showed that tocilizumab tempered the inflammatory response after non-STEMI and diminished the release of TnT, in particular in patients who underwent PCI, suggesting that tocilizumab could mitigate the I/R injury (12).

The ASSAIL-MI trial was a first-in-human, proof-of-concept trial. It was designed to test whether IL-6 receptor inhibition could attenuate the inflammatory overshoot that occurs during MI and reperfusion in patients with acute STEMI and thereby reduce the harmful effects of inflammation. We assumed that a reduction in the I/R injury would be reflected in a larger degree of myocardial salvage, a surrogate endpoint that is associated with clinical outcomes (5). The myocardial salvage index reports myocardial salvage as a fraction of the area at risk, which reduces the otherwise large variability in measures of infarct size and allows for a smaller sample size (15). We showed that tocilizumab improved myocardial salvage and reduced the extent of microvascular obstruction, suggesting that there is a potential for targeted therapy against the inflammatory cytokine IL-6 in these patients.

We assessed the area at risk with early gadolinium enhancement steady-state free precession images. Our data show that the area at risk was numerically smaller in the tocilizumab arm. A recent meta-analysis showed that a reduction in the area at risk was mainly observed in studies in which the intervention reduced the final infarct size (26). Final

FIGURE 3 Primary Outcome in Pre-Specified Subgroups



Primary outcome in pre-specified subgroups (age younger than 60 years vs. at least 60 years, duration from symptom onset to study drug infusion <3 h vs. at least 3 h, female sex vs. male sex, area at risk above median vs. below median, and the areas under the curve [AUC] for troponin T [TnT] and C-reactive protein [CRP] above vs. below median).

TABLE 4 Patients With Serious Adverse Events and Events of Special Interest (6 Months' Follow-Up)

Event	Tocilizumab	Placebo
Any serious adverse event	19	15
Infections requiring hospitalization	3	2
New malignancy	2	0
Cardiovascular events	9	10
Myocardial infarction	0	4
CABG	1	0
Chest pain	5	4
Resuscitated VF	1	1
VT	1	0
Ischemic stroke	0	1
SAH	1	0
Worsening renal function*	0	0
Liver-associated events†	0	0

*Defined as a doubling in serum creatinine from baseline, a >50% fall in the estimated glomerular filtration rate, or the need for renal replacement therapy.
 †Defined as an elevation of aspartate transaminase to above 3 times the upper limit of normal beyond the acute phase or Child Pugh stage II or III liver failure.
 CABG = coronary artery bypass grafting; SAH = subarachnoid hemorrhage; VF = ventricular fibrillation; VT = ventricular tachycardia.

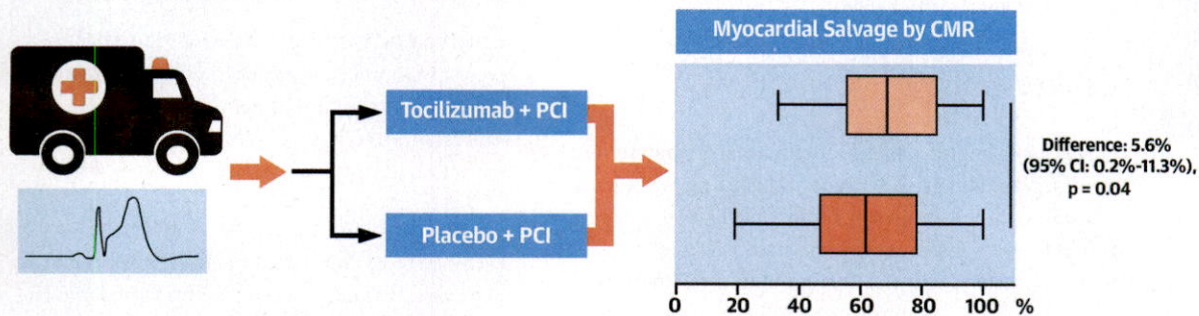
infarct size was also numerically smaller in the group receiving tocilizumab. Whether the modest gain in myocardial salvage can translate into a clinical benefit in patients with STEMI should be confirmed in larger trials with clinical endpoints.

The absolute effect of tocilizumab on myocardial necrosis was smaller than we assumed when we designed the trial. This may explain why there was

no significant reduction in infarct size as measured by CMR or the release of TnT and CK-MB. Although the relative reduction in the median infarct size was 21%, the median infarct size in the placebo arm was limited. We included nonanterior MIs, we randomized patients before evaluating target vessel coronary blood flow, and we excluded patients with <6 h of ischemia, all of which may have contributed to the smaller than expected infarct sizes. The small extent of myocardial necrosis may also explain why at 6 months there were no signs of material left ventricular remodeling in either treatment group, and why, despite the improved myocardial salvage in the tocilizumab arm, there was no between-group difference in NT-proBNP.

Because IL-6 inhibition was untested in STEMI, we selected a modest dose of tocilizumab designed to provide short-lived full suppression of IL-6 signaling. The dose was selected to minimize the potential negative effect on myocardial healing but may have been too small to achieve maximal anti-inflammatory effect. Reassuringly, there were no major safety issues and specifically no myocardial ruptures. On the other hand, we observed a robust reduction in CRP in the tocilizumab arm, suggesting that we achieved powerful inhibition of the IL-6 pathway. However, not all relevant effects of IL-6 are reflected in circulating levels of CRP, and this important issue should be explored in forthcoming studies.

CENTRAL ILLUSTRATION Design and Primary Result of the ASSAIL-MI Trial



Broch, K. et al. *J Am Coll Cardiol.* 2021;77(15):1845-55.

In the ASSAIL-MI trial, we randomized 199 patients with acute ST-segment elevation myocardial infarction (illustrated by ambulance and ST-segment elevation in electrocardiogram) to prompt treatment with the interleukin-6 receptor inhibitor tocilizumab or placebo during percutaneous coronary intervention (PCI). As illustrated in the bar chart, the primary endpoint, the myocardial salvage index as measured by cardiac magnetic resonance imaging (CMR), was higher in patients allocated to tocilizumab (between-group difference 5.6% [95% confidence interval: 0.2% to 11.3%] of left ventricular volume; $p = 0.04$). ASSAIL-MI = ASSEssing the effect of Anti-IL-6 treatment in Myocardial Infarction.

Bearing in mind that the subgroup analyses were exploratory only, the effect on the primary endpoint seemed to be stronger in patients presenting >3 h after symptom onset. It is conceivable that the inflammatory response, and therefore the potential effect of the anti-inflammatory intervention, is smaller in short-lasting ischemia. Prompt revascularization may minimize the area amenable to salvage in patients with a short history of chest pain. For safety reasons, we excluded patients with a time from symptom onset of >6 h, as well as patients with cardiogenic shock or resuscitated cardiac arrest.

STUDY LIMITATIONS. The ASSAIL-MI trial was designed to show the effect of tocilizumab on myocardial salvage in patients presenting with acute STEMI. Investigators have recently questioned the validity of the myocardial salvage index (27); however, the salvage index was a favored endpoint in clinical trials aiming for cardioprotection when the trial was designed. Simulations based on multisite, multivendor data showed that the sample size could be substantially reduced if the effect of the intervention was evaluated by the myocardial salvage index instead of infarct size (15). The number of patients was limited, but the trial was designed to detect a clinically meaningful increase in myocardial salvage. However, the myocardial salvage index was higher than expected in the placebo group, limiting the statistical power of the trial. Immediate and powerful inhibition of inflammation is a novel treatment concept in STEMI, and safety was therefore emphasized. The strict inclusion and exclusion criteria may have limited the effect of the intervention. The narrow inclusion criteria also limit the generalizability of the results.

CONCLUSIONS

Early treatment with tocilizumab augmented myocardial salvage in patients presenting with acute STEMI within 6 h of symptom onset. There was a trend toward less myocardial necrosis and smaller final infarct sizes in the tocilizumab arm. In exploratory subgroup analyses, the effect of tocilizumab seemed to be limited to patients who were randomized >3 h after the onset of symptoms. The drug was well tolerated and there were no major safety

concerns. The clinical significance of the observed increase in myocardial salvage is uncertain. Larger studies should explore the effect of tocilizumab on clinical endpoints, optimize the dose of tocilizumab, and perhaps select patients who present several hours after symptom onset.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a proof-of-concept study, administration of the interleukin-6 receptor inhibitor tocilizumab in patients with acute STEMI was associated with myocardial salvage, as assessed by magnetic resonance imaging.

TRANSLATIONAL OUTLOOK: Larger trials are necessary to confirm whether inhibition of inflammation ameliorates post-ischemic myocardial reperfusion injury and improves clinical outcomes in patients with acute STEMI.

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KEY WORDS inflammation, infarct size, myocardial salvage, randomized controlled trial, reperfusion injury, ST-segment elevation myocardial infarction

APPENDIX For supplemental tables, please see the online version of this paper.

EDITORIAL COMMENT

Inhibiting Interleukin-6 to Reduce Cardiovascular Event Rates



A Next Step for Atherothrombosis Treatment and Prevention*

Paul M Ridker, MD, MPH

In the rapidly evolving story of inflammation and atherothrombosis, all roads seem to converge on interleukin (IL)-6, a central signaling cytokine of innate immunity (1). More than 20 years ago, major epidemiological studies demonstrated that baseline levels of IL-6 are as powerful a predictor of future vascular events as are levels of low-density lipoprotein cholesterol (2), a phenomenon that continues to this day (3). Genome-wide association studies demonstrate that random allocation of alleles that control IL-6 signaling associate with lifelong increased cardiovascular risk (4), while phenome-wide association studies link IL-6 to the development of peripheral arterial disease, aortic aneurysm, and stroke (5). Abundant bench data spanning the same 2 decades has long suggested multiple mechanisms linking IL-6 to plaque erosion and rupture, including activation of matrix metalloproteinases that weaken the fibrous cap, activation of endothelial cells to over-express adhesion molecules, and the induction of tissue factor leading to a prothrombotic environment. But it was not until 2017 that the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) provided definitive proof that reducing inflammation in the canonical IL-1b to -6 pathway of innate immunity reduces cardiovascular event rates (6). Crucially, CANTOS demonstrated that the magnitude of benefit associated with targeted inflammation inhibition was

directly related to the magnitude of IL-6 reduction achieved (7). Two recent positive trials of colchicine cement for the cardiovascular community that safe and inexpensive anti-inflammatory therapies for chronic stable atherosclerosis have arrived (8,9).

A second frontier for inflammation inhibition has been in the setting of acute coronary ischemia and reperfusion injury, where it has also long been known that inflammatory biomarkers including IL-6 associate with poor cardiovascular outcomes (10). Astute clinical observation from a randomized trial conducted in unstable angina demonstrated long ago that individuals with elevated IL-6 benefited greatly and had reduced mortality from an early invasive reperfusion strategy, whereas those with lower IL-6 levels did not (11). Addressing direct IL-6 intervention for the first time, Kleaveland et al. (12) presented in 2016 a small but intriguing phase 2 study of tocilizumab, a monoclonal antibody that inhibits the binding of IL-6 to its receptors, in patients with non-ST-segment elevation myocardial infarction (STEMI). Tocilizumab is an agent approved by the U.S. Food and Drug Administration that is commonly used to treat rheumatoid arthritis and cytokine release syndromes. In this preliminary study of non-STEMI patients, tocilizumab showed an anticipated reduction in C-reactive protein, suggested a modest reduction in percutaneous coronary intervention-related troponin release, and provided enough initial safety data to keep the field moving forward (12).

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Center for Cardiovascular Disease Prevention and the Divisions of Preventive Medicine and Cardiovascular Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

SEE PAGE 1845

In this issue of the *Journal*, Broch et al. (13), working in the same research group, extend this concept to STEMI in a randomized trial of a single dose of tocilizumab (280 mg intravenous vs. placebo) given within 6 h of presentation. Among 199 patients at 3 quality high-volume Norwegian centers, stratified by time from symptom onset <3 or >3 h, the authors report tocilizumab compared with placebo to

be associated with a modest increase in the myocardial salvage index measured by cardiac magnetic resonance imaging at 3 to 6 days (trial primary endpoint 5.6% improvement; $p = 0.04$), although without a statistically significant effect on final infarct size measured at 6 months (7.2% vs. 9.1%; $p = 0.08$). Secondary endpoints included a significant reduction in microvascular obstruction ($p = 0.03$), a nonsignificant difference in area under the troponin curve ($p = 0.13$), a significant reduction of C-reactive protein during index hospitalization ($p < 0.001$), but without effect on N-terminal pro-B-type natriuretic peptide ($p = 0.25$) or end-diastolic volume at 6 months ($p = 0.54$). As known to occur with tocilizumab, there were small increases in atherogenic lipids, triglycerides, and liver enzymes and modest reductions in neutrophil and monocyte counts.

Taken together, these 2 hypothesis-generating studies in STEMI and non-STEMI patients are important and could portend the future to come. Moving anti-inflammatory interventions from stable atherosclerosis into acute ischemia is of considerable clinical relevance, although mechanisms likely differ and relate more to ischemia/reperfusion injury and the consequences of plaque rupture than to atherosclerotic progression. For example, although colchicine appears to be effective in the setting of chronic stable angina, a trial of colchicine initiation at the time of acute coronary ischemia did not show significant benefit on long-term cardiovascular outcomes (14). By contrast, from a safety perspective, no cases of myocardial rupture have been noted in these studies, suggesting that acute anti-inflammatory therapy is unlikely to adversely affect short-term myocardial healing.

By their nature, small studies leave many questions unanswered. Although the current STEMI analysis is statistically positive for the primary endpoint of myocardial salvage index, the magnitude of effect is small (5.6%) and quite a bit less than the 20% typically used to define clinical importance. The subgroup observation that benefit was observed on the primary endpoint for those treated after 3 h of symptom onset but not within 3 h could be informative about inflammation as it relates to reperfusion injury, but it might also prove to be a chance finding. Similarly, the observation of benefit among men but not women could represent biological signal or insufficient evidence. Such issues, crucial to guide future work, require external validation.

Moving IL-6 inhibitors into cardiovascular practice will not be free of controversy (15). Currently available IL-6 inhibitors fall into 2 broad classes, monoclonal antibodies that target the IL-6 receptor (such as tocilizumab and sarilumab) and monoclonal

antibodies that target the IL-6 ligand (such as sirukumab and siltuximab). When used among patients with rheumatoid arthritis and other systemic immunological disorders, these agents have been associated with modest neutropenia, elevations of hepatic enzyme levels, and lipid elevations. Investigators will also need to clarify whether "classical" IL-6 signaling via membrane-bound IL-6 receptors on hepatocytes and some leukocytes has similar or different atherothrombotic effects when compared with "trans" IL-6 signaling that occurs on a more systemic basis in multiple peripheral tissues.

Nonetheless, the potential for benefit is also very large and the pharmaceutical industry is paying attention to this arena. Ziltivekimab, a novel IL-6 ligand monoclonal antibody, has recently been investigated in phase 2 clinical trials and is being developed primarily as an agent to inhibit atherosclerotic progression. A patient population to consider for an initial cardiovascular outcomes trial targeting IL-6 would be those with chronic kidney disease, where absolute vascular risk is high and the role of residual inflammatory risk prominent. Chronic kidney disease is a setting where colchicine, a renally excreted drug, cannot easily be given, and thus, renal patients have considerable unmet need.

In summary, moving beyond IL-1b blockade as done in CANTOS to direct downstream inhibition of IL-6 represents a logical next scientific step in the development of anti-inflammatory therapies for both acute ischemia and chronic atherosclerosis. Preventive cardiologists, however, need not wait until outcome trials are complete to use this evolving biological knowledge to their patient's advantage. As recently confirmed in the pages of the *Journal*, exercise, smoking cessation, and a healthy diet reduce both C-reactive protein and IL-6, and clearly have lifelong benefits (16). Our immediate task is thus to incorporate inflammation inhibition through lifestyle management into our daily practice.

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KEY WORDS infarct size, inflammation, myocardial salvage, randomized controlled trial, reperfusion injury, ST-segment elevation myocardial infarction