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

Brief title: ASSAIL-MI

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Funding: This work was supported by the South-Eastern Norway Regional Health Authority, the Central Norway Regional Health Authority, and Roche™. Roche™ provided the investigational medicinal products and an unrestricted grant. Trial registration number: ClinicalTrials.gov (NCT03004703NCT3004703)
Disclosures: Dr Gullestad has received lecture fees from AstraZeneca, Boehringer Ingelheim, Novartis and Amgen and has been a member of local advisory board in AstraZeneca and Boehringer Ingelheim. The other authors do not have conflicts of interest pertaining to this work.

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Tweet: The ASSAIL-MI trial showed that inhibition of inflammation could reduce cardiac damage after treatment for acute myocardial infarction.

Acknowledgements
This study was supported by an independent grant from ROCHE who also provided drugs/placebo for infusion. We thank professors Eirik Skogvoll, Jan Erik Nordrehaug and Terje Steigen on the data safety monitoring board, and Rita Skårdal, who prepared the study drugs. We are grateful to Bjørn Solvang, Bethany Kirsten Danielsen, Inger Tvenning and Anne Caroline Wiik for providing clinical research support and monitoring. We acknowledge Hans Kristian Wethal and Dag Erik Godø for their participation in enrolling patients at the Ullevål site, and Hege Synnøve Claussen and Sissel Åkra for blood sampling and preparation.

Abstract
Background: Prompt myocardial revascularization with percutaneous coronary intervention (PCI) reduces infarct size and improves outcomes in patients with ST-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: We designed the ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction (ASSAIL-MI) trial 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 three high-volume PCI centers in Norway. Patients admitted with STEMI within six hours 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 three to seven 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 – 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 versus 9.1 % of myocardial volume, p = 0.08). Adverse events were evenly distributed across the treatment groups.
Conclusion: Tocilizumab increased myocardial salvage in patients with acute STEMI.

Condensed abstract
Inflammation may prevent the salvage of viable myocardial tissue after coronary revascularization for myocardial infarction. We performed a randomized controlled trial designed to assess the effect of immediate anti-inflammatory treatment with the interleukin-6 receptor inhibitor tocilizumab on myocardial salvage in acute ST-elevation myocardial infarction. The primary endpoint, the myocardial salvage index as measured by magnetic resonance imaging 3 – 7 days after the intervention, was 5.6 percentage points higher in the tocilizumab arm (p = 0.04). Our results suggest that anti-inflammatory treatment may improve myocardial salvage after percutaneous coronary intervention for myocardial infarction.

Key words: ST-elevation myocardial infarction; Reperfusion injury; Inflammation; Infarct size; Myocardial salvage, Randomized controlled trial

Abbreviations
ASSAIL-MI = ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction
CMR = cardiac magnetic resonance imaging
CRP = C-reactive protein
I/R = ischemia/reperfusion
MI = myocardial infarction
NT-proBNP = N-terminal pro-B-type natriuretic peptide
PCI = percutaneous coronary intervention
SSFP = steady-state free precession
STEMI = ST-elevation myocardial infarction
TnT = cardiac troponin T

Introduction

The mortality and morbidity associated with ST-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, i.e. 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 hours 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 more than 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 *ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction* (ASSAIL-MI) trial to test the hypothesis that prompt administration of tocilizumab would increase the myocardial salvage index in patients presenting with acute STEMI (13).

Methods

Trial design and participants

This phase II, parallel arm, double blind, randomized, placebo-controlled trial was conducted at three 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 six hours of symptom onset and ST-segment elevation in two contiguous electrocardiogram leads consistent with acute transmural MI (14). Key exclusion criteria were previous MI; left bundle branch block; cardiogenic shock; resuscitated cardiac arrest; fibrinolytic therapy within the last 72 hours; a history of severe renal failure, liver failure, malignant disease, chronic infection or chronic autoimmune or inflammatory disease; uncontrolled bowel disease; ongoing infectious or immunologic disease; major surgery within the last 8 weeks; or treatment with immunosuppressants other than low-dose steroids

(equivalent to a systemic exposure to 5 mg prednisone/day). Detailed inclusion and exclusion criteria are provided in Supplementary 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 enrolment, 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 prior to 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 one hour, 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 three hours. Patients, study personnel and care takers 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 less than three hours or three hours 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 $\left(\frac{Area\ at\ risk - infarct\ size}{Area\ at\ risk}\right)$ x 100 measured by CMR three to seven 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. Prespecified secondary endpoints included i) final infarct size (in % of left ventricular mass) as measured by CMR six months after the intervention, ii) microvascular obstruction iii) the area under the curve for TnT and iv) CRP during index hospitalization, v) N-terminal pro-B-type natriuretic peptide (NT-proBNP) and vi) baseline-adjusted left ventricular end-diastolic volume at six months, and vii) safety and tolerability. For details, see Supplementary 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 and MITOCARE 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 ± standard deviation for the myocardial salvage index was 54.0 ± 19.4 %, and the mean ± standard deviation of the infarct size was 17.4 ± 10.5 % of left ventricular mass.

With a standard deviation of 20 % and 2 x 100 patients, our trial has 90% power to statistically detect an underlying treatment effect on the myocardial savage 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 three 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 72-168 hours after admission as well as after three and six months. CMR was performed at three to seven days, and at six 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 five minutes, we acquired a stack of short-axis images of the left ventricle using a retrospectively ECG-gated, steady-state free precession (SSFP) 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 x 1.5 mm, and the temporal resolution 30-35ms. After fifteen minutes, corresponding late enhancement images were acquired in the same image positions (inversion recovery FLASH). The same protocol was used at the six-month exam.

All CMR images were analyzed by a core lab 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 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 (ELICA; 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 ± standard deviation or median (interquartile range) if distributions were skewed. Categorical data are reported as a 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 six prespecified subgroups that were analyzed individually and then in a multivariable model. The following a-priori subgroup analyses were planned: age under versus over 60 years, duration from symptom onset to study drug infusion less than versus at least three hours, 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. Two-sided probability values were considered significant at $p < 0.05$. 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.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. The named authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 16th March 2017 and 13th February 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/her data. In four patients, the CMR at three to seven 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 minutes. All patients underwent primary PCI except for eight patients who were deemed not to have MI, five patients in the tocilizumab arm and three 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 ($p = 1.00$). One hundred and ninety-five patients attended the six-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 six months' 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 ± 19 % versus 64 ± 21 %). The between-group difference was 5.6 percentage points (95 % confidence interval 0.2 – 11.3); p = 0.04 (Figure 2). The median final infarct size measured six 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 exams are provided in Table 3 and the laboratory analyses in Supplementary table 3.

The primary outcome in the six prespecified 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 more than three hours 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 six 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 were three infections requiring prolongation of the index hospitalization or renewed hospitalization in the tocilizumab arm and two 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 two 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 three and six 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 more than three hours 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. While 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 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 NSTEMI 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-trial was a first-in-man, 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 number of patients with 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 SSFP-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 where the intervention reduced the final infarct size (26). Final 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. While the relative reduction in the median infarct size was 21 %, the median infarct size in the placebo arm was limited. We included non-anterior myocardial infarctions, we randomised patients prior to evaluating target vessel coronary blood flow, and we excluded patients with less than six hours 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 six 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.

Bearing in mind that the subgroup analyses were exploratory only, the effect on the primary endpoint seemed to be stronger in patients presenting more than three hours 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 above six hours, as well as patients with cardiogenic shock or resuscitated cardiac arrest.

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 multi-site, multi-vendor 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.

Conclusion

Early treatment with tocilizumab augmented myocardial salvage in patients presenting with acute STEMI within six hours of symptom onset. There was a trend towards 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 more than three hours 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.

Perspectives

Competency in Medical Knowledge: In a proof-of-concept study, administration of the Interleukin-6 receptor inhibitor tocilizumab in patients with acute ST-elevation myocardial infarction (STEMI) was associated with increased 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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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-elevation myocardial infarction

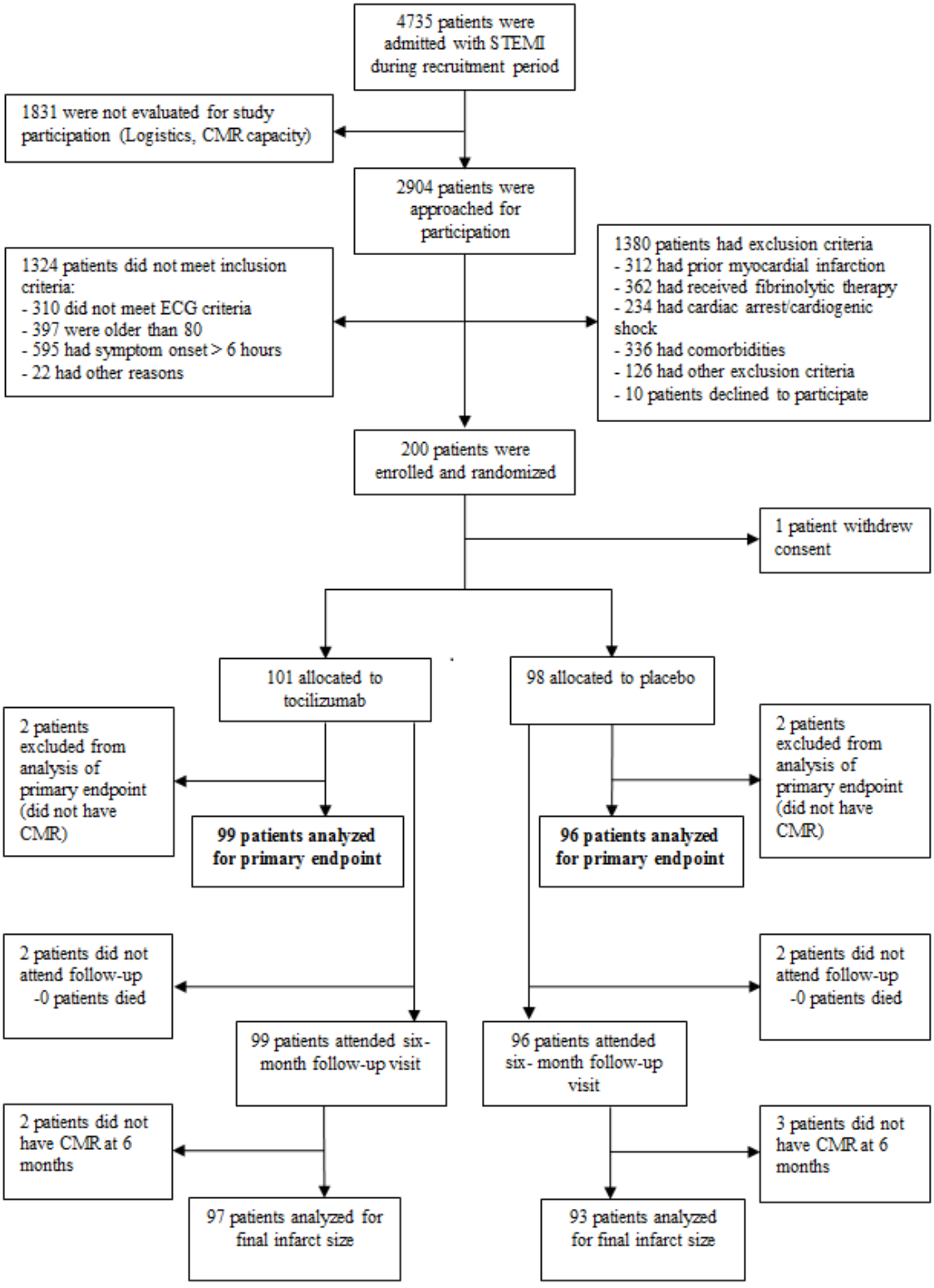


Figure 2 Myocardial salvage

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

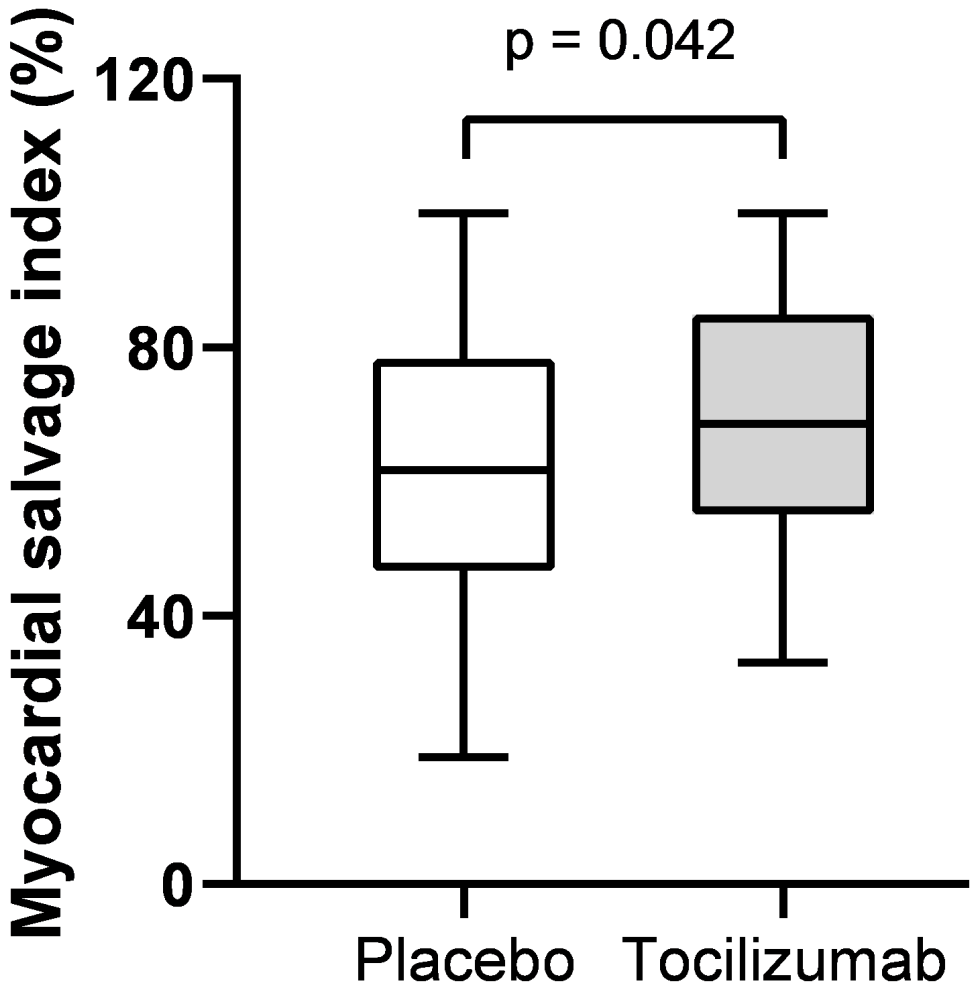
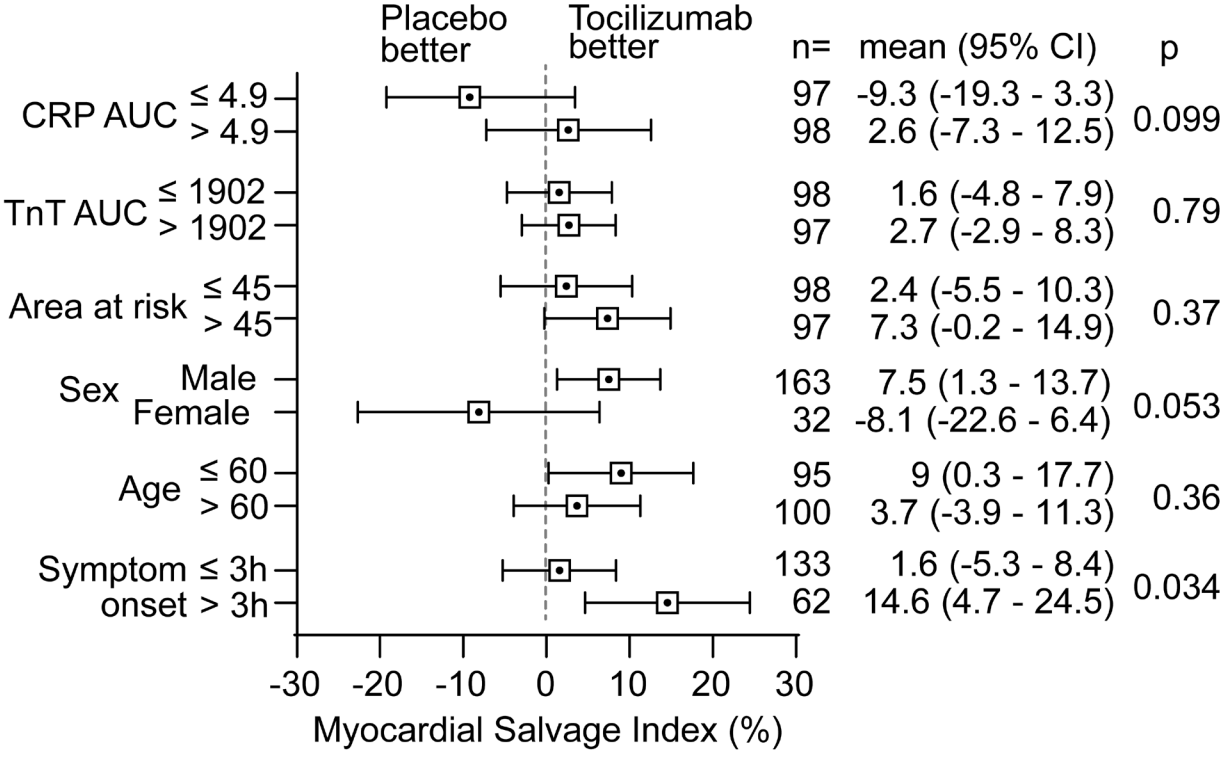


Figure 3 Primary outcome in prespecified subgroups

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



Central illustration:

Caption: Design and primary result of the ASSAIL-MI trial

Legend: In the ASSAIL-MI trial, we randomized 199 patients with acute ST-elevation myocardial infarction (illustrated by ambulance and ST-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 – 11.3] % of left ventricular volume; p = 0.04).

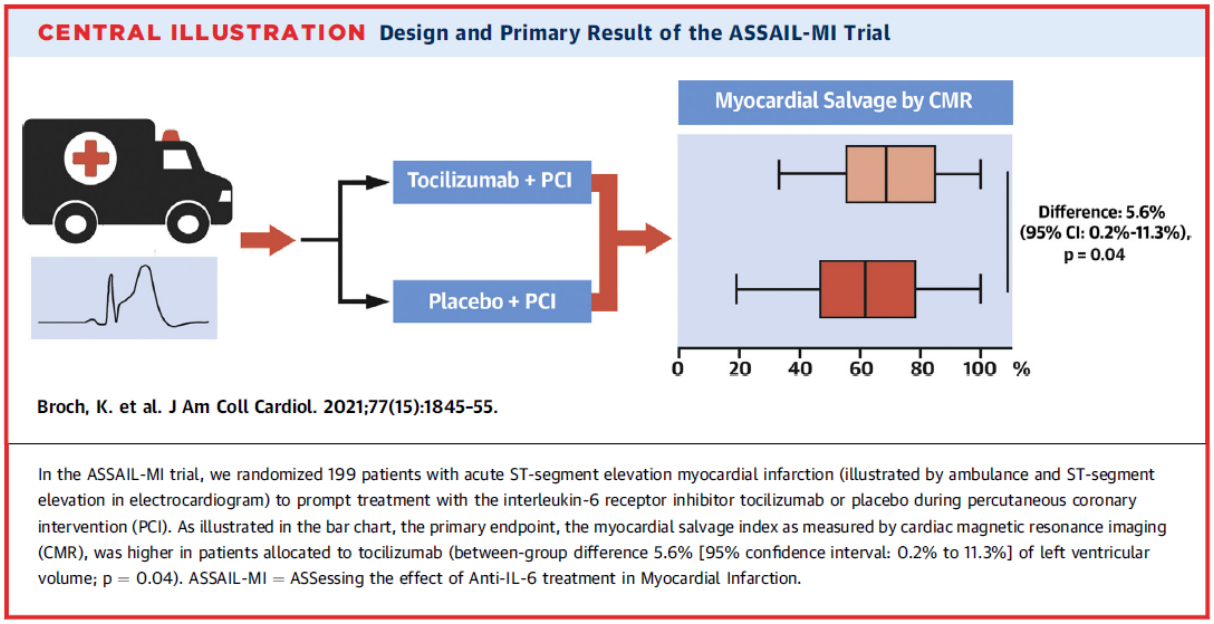


Table 1: Baseline characteristics

Variable	Tocilizumab (N = 101)	Placebo (N = 98)
Demography		
Age – years	62 ± 10	60 ± 9
Men – no (%)	80 (79)	87 (89)
Body mass index – kg/m^2	27.1 ± 4.5	27.5 ± 4.3
Caucasian race – no (%)	99 (98)	94 (96)
Smoking status – no (%)		
Never smokers	38 (38)	36 (37)
Previous smokers	33 (33)	24 (24)
Current smokers	30 (30)	38 (39)
Prior conditions – no (%)		
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 – no (%)		
ACEI[*] 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 - mmHg		
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[**]	151 ± 71	149 ±72
center – min		
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
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 ± 13	144 ± 12
Platelet count – 10^9/l	253 ± 59	260 ± 62

Total white blood cell count – 10^9/l	11.6 ± 3.4	11.6 ± 3.4
Aspartate transaminase – U/l	28 (22-37)	30 (24-37)
Troponin T – ng/l	44 (22-163)	49 (28-95)
CK-MB[‡] – ug/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 ± 17	78 ± 20
Glucose – mmol/l	9 ± 3	9 ± 3
HbA1c – mmol/mol	37 (34-41)	37 (34-40)
Total cholesterol – mmol/l	5.3 ± 1.2	5.2 ± 1.0
HDL[?] cholesterol – mmol/l	1.2 (0.9-1.3)	1.1 (0.9-1.3)
LDL[#] cholesterol – mmol/l	3.7 ± 1.1	3.7 ± 0.9
C-reactive protein – mg/l	2.4 (0.9-5.0)	2.9 (1.4-5.0)
Albumin – g/l	42 ± 3	42 ± 3

Baseline characteristics stratified by treatment allocation. Values are presented as mean ± SD, median (interquartile range) or number (%) as appropriate. [*]ACEI = angiotensin converting enzyme inhibitor; [†]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.

Table 2 Primary and secondary outcomes

	Tocilizumab	No of patients	Placebo	No of patients	Between-group difference (95 % CI)	p-value*
Myocardial salvage index - %	69.3 ± 19.3	99	63.6 ± 20.8	96	5.6 (0.2 – 11.3)	0.04
Final infarct size at 6 months (% of left ventricular mass)	7.2 (2.6 – 11.8)	97	9.1 (2.9 – 16.3)	93	-	0.08
Extent of microvascular obstruction (% of left ventricular volume)	0 (0 - 14)	99	4 (0 - 18)	96	-	0.03
Troponin T AUC† - ng/l/h	1614 (860 – 3515)	101	2357 (973 – 4127)	98	-	0.13
C-reactive protein AUC† - mg/l/h	1.9 (0.9 – 4.9)	101	8.6 (5.0 – 17.9)	98	-	<0.001
Baseline-adjusted LVEDV‡ at 6 months - ml	157 (151 – 166)	97	160 (153 – 166)	93	3 (-6 – 11)	0.54
NT-proBNP§ at 6 months (ng/l)*	79 (50 – 187)	98	63 (50 – 148)	97	32 (-84 – 149)	0.25

Primary and secondary endpoints. Values are presented as mean ± SD and median (interquartile range) as appropriate.

*We did not adjust for multiple testing, and all p-values are nominal only. †AUC = area under the curve. ‡LVEDV = left ventricular end diastolic volume. §NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Table 3 Cardiac magnetic resonance imaging data

	3 – 7 days after randomization			6 months after randomization		
	Tocilizumab	Placebo	p for difference	Tocilizumab	Placebo	p 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# – no (%)	35 (35)	49 (51)	0.02	10 (10)	11 (12)	0.46

Data are presented as mean ± standard deviation or median (interquartile range) depending on distribution. *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

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 more than 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 II liver failure. CABG = coronary artery bypass grafting; SAH = Subarachnoid hemorrhage; VF = ventricular fibrillation; VT = ventricular tachycardia.