

ORIGINAL ARTICLE

Cyclosporine before PCI in Patients with Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

Experimental and clinical evidence suggests that cyclosporine may attenuate reperfusion injury and reduce myocardial infarct size. We aimed to test whether cyclosporine would improve clinical outcomes and prevent adverse left ventricular remodeling.

METHODS

In a multicenter, double-blind, randomized trial, we assigned 970 patients with an acute anterior ST-segment elevation myocardial infarction (STEMI) who were undergoing percutaneous coronary intervention (PCI) within 12 hours after symptom onset and who had complete occlusion of the culprit coronary artery to receive a bolus injection of cyclosporine (administered intravenously at a dose of 2.5 mg per kilogram of body weight) or matching placebo before coronary recanalization. The primary outcome was a composite of death from any cause, worsening of heart failure during the initial hospitalization, rehospitalization for heart failure, or adverse left ventricular remodeling at 1 year. Adverse left ventricular remodeling was defined as an increase of 15% or more in the left ventricular end-diastolic volume.

RESULTS

A total of 395 patients in the cyclosporine group and 396 in the placebo group received the assigned study drug and had data that could be evaluated for the primary outcome at 1 year. The rate of the primary outcome was 59.0% in the cyclosporine group and 58.1% in the control group (odds ratio, 1.04; 95% confidence interval, 0.78 to 1.39; $P=0.77$). Cyclosporine did not reduce the incidence of the separate clinical components of the primary outcome or other events, including recurrent infarction, unstable angina, and stroke. No significant difference in the safety profile was observed between the two treatment groups.

CONCLUSIONS

In patients with anterior STEMI who had been referred for primary PCI, intravenous cyclosporine did not result in better clinical outcomes than those with placebo and did not prevent adverse left ventricular remodeling at 1 year. (Funded by the French Ministry of Health and NeuroVive Pharmaceutical; CIRCUS ClinicalTrials.gov number, NCT01502774; EudraCT number, 2009-013713-99.)

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OVER THE PAST THREE DECADES, MAJOR progress has been made in the treatment of patients with ST-segment elevation myocardial infarction (STEMI).¹ Nevertheless, the rates of death, heart failure, and recurrent ischemic events occurring in the first year after infarction remain unacceptably elevated in this high-risk population. Although many advances have been made in the development of methods to reopen the culprit coronary artery and prevent reocclusion, there is currently no specific treatment that targets myocardial reperfusion injury, which is a paradoxical form of myocardial damage that occurs as a result of the restoration of vessel patency.² Growing evidence from experimental studies and small-size proof-of-concept clinical trials shows that reperfusion injury contributes greatly to the final infarct size.³⁻⁵ Preclinical studies indicate that the opening of the mitochondrial permeability transition pore (PTP) in the inner mitochondrial membrane plays a major role in reperfusion injury.^{6,7} Either genetic or pharmacologic inhibition of cyclophilin D, a major component of the PTP, reduces the severity of myocardial reperfusion injury.⁸⁻¹⁰

Cyclosporine is a pharmacologic inhibitor of cyclophilin D. In a proof-of-concept phase 2 trial, we found that the administration of cyclosporine immediately before primary percutaneous coronary intervention (PCI) reduced the myocardial infarct size in patients with STEMI.¹¹ In the current phase 3 trial, we investigated whether a single intravenous dose of cyclosporine, administered immediately before PCI, would improve clinical outcomes and prevent adverse left ventricular remodeling at 1 year in patients with anterior STEMI.

METHODS

STUDY DESIGN

The Does Cyclosporine Improve Clinical Outcome in ST Elevation Myocardial Infarction Patients (CIRCUS) trial was an international, investigator-driven, multicenter, randomized, double-blind, placebo-controlled trial, which was coordinated by the Hospices Civils de Lyon.¹² This trial was performed in accordance with the principles of the Declaration of Helsinki and the European guidelines for Good Clinical Practice. Approval was obtained from the ethics committees in the relevant countries.

The study was supported by a grant from the French Ministry of Health. NeuroVive Pharmaceutical provided the study drug at no charge, as well as supplementary funding to allow for the inclusion of study sites in Belgium and Spain. The funders had no role in the design of the study, the collection, monitoring, analysis, or interpretation of the data, or the writing of the report.

The authors designed and coordinated the trial, oversaw the study conduct and reporting, managed the database, and wrote all drafts of the manuscript. All the authors vouch for the accuracy and completeness of the data and the analyses reported and for the fidelity of the study to the trial protocol, which is available with the full text of this article at NEJM.org.

STUDY POPULATION

Patients eligible for enrollment were men and women, 18 years of age or older, who presented within 12 hours after the onset of symptoms that were consistent with an acute coronary syndrome, who had ST-segment elevation of 0.2 mV or more in two contiguous anterior leads, and for whom the clinical decision was made to treat with PCI. It was also required for trial eligibility that the culprit coronary artery was the left anterior descending coronary artery, with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0 or 1 at the time of diagnostic coronary angiography. Patients with cardiogenic shock at admission and those with evidence of coronary collateral vessels (Rentrop score of 2 or 3 for the region at risk) on initial coronary angiography were excluded. (A Rentrop score of 0 indicates no filling of any collateral channels; 1, filling by collateral vessels of side branches of the artery to be perfused without visualization of the epicardial segment; 2, partial filling of the epicardial artery by collateral vessels; and 3, complete filling of the epicardial artery by collateral vessels.) The complete inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent before inclusion in the study.

PCI AND STUDY TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive cyclosporine or placebo (control group). Randomization with stratification according to study center was performed after the initial coro-

nary angiography, with the use of a secure 24-hour computerized central system.

The investigational product was a lipid emulsion formulation of cyclosporine (CicloMulsion, NeuroVive Pharmaceutical),¹³ administered intravenously at a dose of 2.5 mg per kilogram of body weight. The control group received a matching placebo formulation. In each group, the study drug was infused over a period of 2 to 3 minutes by means of a catheter positioned within an antecubital vein, before the PCI procedure.

Patients underwent PCI according to standard guidelines.¹⁴ The use of thrombus aspiration, bare-metal or drug-eluting stents, and glycoprotein IIb/IIIa inhibition was left to the discretion of the treating physician.

STUDY OUTCOMES

Our initial plan was to use the composite of death or rehospitalization for heart failure as the primary outcome. We estimated that the required sample would be 3862 patients. Owing to limited funding, it was necessary to redesign the trial with a smaller sample size. We therefore chose to add two additional outcomes to the primary composite outcome — worsening of heart failure during the initial hospitalization and adverse left ventricular remodeling. These two components were chosen because there is a pathophysiological link among infarct size, adverse left ventricular remodeling, heart failure, and survival and because worsening of heart failure can be observed after PCI reperfusion in patients with STEMI. The decision to revise the primary outcome and reduce the necessary sample size was taken before the enrollment of any patients in the trial. Details are provided in the Supplementary Appendix.

The resulting primary efficacy outcome was a composite of death from any cause, worsening of heart failure during the initial hospitalization (i.e., the index STEMI hospitalization for each patient), rehospitalization for heart failure, and adverse left ventricular remodeling within 1 year. The definition of adverse left ventricular remodeling was set as an increase of 15% or more in the left ventricular end-diastolic volume.¹⁵ Definitions of heart-failure events and echocardiographic methods for the determination of left ventricular remodeling are provided in the Supplementary Appendix.

Secondary outcomes included changes in left

ventricular ejection fraction and left ventricular end-diastolic and end-systolic volumes as assessed during the initial hospitalization and at 1 year, as well as all the individual components of the primary outcome, recurrent acute myocardial infarction, unstable angina, and stroke. All the clinical events were adjudicated by an events-validation committee whose members were unaware of the study-group assignments.

Electrocardiographic and coronary angiographic data were stored digitally and sent to a central core laboratory for analysis. The area at risk according to angiography was determined at baseline and after PCI as described in the Supplementary Appendix. The total creatine kinase level was measured locally at admission and at 4, 12, and 24 hours after reperfusion. Safety assessments included the measurement of the creatinine and blood glucose levels and the white-cell count at baseline and at 48 hours.

STATISTICAL ANALYSIS

We estimated that the event rates in the control group over the planned 12 months of the study would be 7% for death from any cause and 42% for the combined outcome of heart failure or left ventricular remodeling. We estimated that 790 patients (395 patients per group) would be required for the study to have 80% power to detect a 20% lower relative risk in the cyclosporine group than in the placebo group, at a two-sided alpha level of 5%. From the literature, we estimated that the assessment of left ventricular remodeling would be missing for 14% of patients surviving at 1 year, and the sample size was increased to adjust for missing values.¹⁵ The sample size was increased by a further 10% to accommodate the fact that the sample size was calculated assuming the use of a chi-square test, whereas a different model was used for the analysis. The final sample size was estimated to be 972 patients. The sample size was calculated with the use of nQueryAdvisor+nTerim software, version 2.0 (Statistical Solutions).

For baseline and procedural characteristics, data are presented for all the patients who underwent randomization. For the primary analysis, a modified as-treated analysis was prespecified to include all the patients who underwent randomization, received the study drug, and had a valid measurement for the primary outcome. A per-protocol analysis was also prespecified.

The population for the per-protocol analysis is defined in the Supplementary Appendix.

For the primary outcome, we compared the proportion of patients in the cyclosporine group versus the control group who had at least one component event of the primary composite efficacy outcome at 1 year by using a logistic mixed-effect regression model that included treatment as a fixed effect and center as a random effect. For each component of the primary outcome and for secondary clinical outcome events such as myocardial infarction, unstable angina, and stroke, similar methods were used without correction for multiple testing. All the reported subgroup analyses were prespecified before the database was locked and are listed in the statistical analysis plan (available with the protocol at NEJM.org).

RESULTS

CHARACTERISTICS OF THE PATIENTS, PROCEDURAL CHARACTERISTICS, AND HOSPITAL COURSE

From April 2011 through February 2014, a total of 970 patients were enrolled at 42 hospitals in three countries, with 475 patients assigned to the cyclosporine group and 495 to the control group. The intention-to-treat analysis included all these patients except for 1 in the cyclosporine group who did not provide written informed consent. Of the 970 patients, 960 (99.0%) received the randomized treatment (469 patients in the cyclosporine group and 491 in the control group). The modified as-treated analysis included all the patients who underwent randomization, received the study drug, and had a valid measurement for the primary outcome (395 patients in the cyclosporine group and 396 in the control group) (Fig. 1). The per-protocol analysis included 345 patients in the cyclosporine group and 336 patients in the control group.

The baseline characteristics of all the trial participants are shown in Table 1, and the procedural characteristics are shown in Table 2. These characteristics were well balanced between the two groups, except for the proportion of smokers, which was lower in the cyclosporine group than in the control group (39.0% vs. 45.7%, $P=0.03$) (Table 1), and the proportion of patients with multivessel disease, which was higher in the cyclosporine group than in the control group (40.9% vs. 33.1%, $P=0.01$) (Table 2).

The size of the area at risk and the proportion of patients with a TIMI flow grade of 2 or 3 after PCI were similar in the two groups. The baseline and procedural characteristics of the modified as-treated population (the primary analysis population) were also similar in the two groups (Tables S1 and S2 in the Supplementary Appendix).

The status of the patients with respect to clinical heart failure after PCI and the initial treatment of the patients in the coronary care unit were similar in the two groups (Table S3 in the Supplementary Appendix). The medications at discharge were also similar in the two groups (Table S4 in the Supplementary Appendix).

CREATINE KINASE AND ELECTROCARDIOGRAPHIC DATA

There was no significant between-group difference in the value of total creatine kinase at any time point (Table S5 in the Supplementary Appendix). The peak value was 3992 IU per liter (interquartile range, 1910 to 5447) in the cyclosporine group and 3917 IU per liter (interquartile range, 1878 to 5608) in the control group. There was also no significant difference between the two groups with respect to the extent of ST-segment elevation at baseline, after PCI, at discharge, or at 1 year (Table S6 in the Supplementary Appendix).

ECHOCARDIOGRAPHIC DATA

Echocardiographic data were not available for 74 of 474 patients (15.6%) in the cyclosporine group and for 95 of 495 (19.2%) in the control group, owing to missing or poor-quality recordings (Fig. 1). There was no significant difference between the two groups with respect to left ventricular ejection fraction or left ventricular end-diastolic or end-systolic volumes at any time point (Table S7 in the Supplementary Appendix).

EFFICACY AND SAFETY

A total of 7 patients were lost to follow-up at 1 year. A primary outcome event occurred in 233 of 395 patients (59.0%) in the cyclosporine group and in 230 of 396 (58.1%) in the control group (odds ratio in the cyclosporine group, 1.04; 95% confidence interval [CI], 0.78 to 1.39; $P=0.77$) (Table 3). All-cause mortality at 1 year was 7.1% in the cyclosporine group and 6.6% in the control group (odds ratio, 1.09; 95% CI, 0.63 to 1.90; $P=0.76$). The rate of initial worsening of heart failure or rehospitalization for heart failure

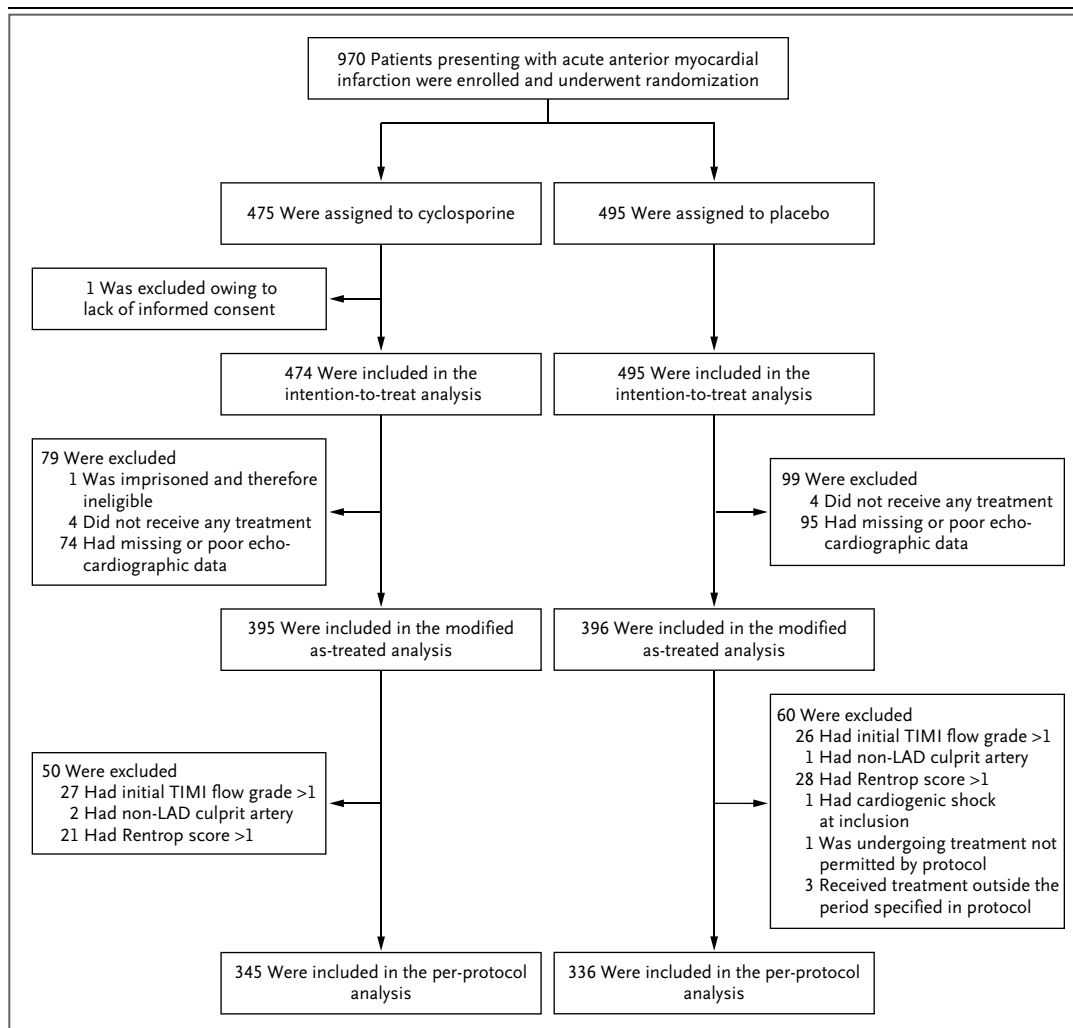


Figure 1. Randomization of Patients and Inclusion in the Intention-to-Treat, Modified As-Treated, and Per-Protocol Analyses.

The intention-to-treat population included all the patients who underwent randomization except for one patient in the cyclosporine group who did not provide written informed consent; the modified as-treated population included all the patients who underwent randomization, received the study drug, and had a valid measurement for the primary outcome. The population for the per-protocol analysis is defined in the Supplementary Appendix. Scores on the Rentrop classification range from 0 to 3, with higher scores indicating greater degree of collateral circulation. A score of 0 indicates no filling of any collateral channels; 1, filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment; 2, partial filling of the epicardial artery by collateral vessels; and 3, complete filling of the epicardial artery by collateral vessels. LAD denotes left anterior descending, and TIMI Thrombolysis in Myocardial Infarction.

at 1 year was similar in the cyclosporine group and the control group (22.8% and 22.7%, respectively; odds ratio, 1.01; 95% CI, 0.72 to 1.41; $P=0.97$). Adverse left ventricular remodeling occurred in 42.8% of the patients in the cyclosporine group and in 40.7% of those in the control group (odds ratio, 1.09; 95% CI, 0.82 to 1.46; $P=0.53$). The combined incidence of death, heart-

failure worsening, and rehospitalization for heart failure at 1 year was similar in the two groups (Fig. 2). The rates of all other secondary clinical outcomes, including cardiogenic shock, recurrent myocardial infarction, unstable angina, stroke, and acute renal failure, were similar in the two groups at 1 year (Table 3).

The results of the per-protocol analysis were

Table 1. Characteristics of the Patients at Baseline.*

| Characteristic | Cyclosporine (N=474) | Control (N=495) |
|---|----------------------|-----------------|
| Age — yr | 60.4±13.1 | 59.5±12.7 |
| Male sex — no. (%) | 399 (84.2) | 396 (80.0) |
| Body-mass index† | 26.9±4.3 | 26.8±4.1 |
| Killip class at admission — no./total no. (%) | | |
| I | 369/422 (87.4) | 381/437 (87.2) |
| II | 45/422 (10.7) | 41/437 (9.4) |
| III | 6/422 (1.4) | 10/437 (2.3) |
| IV | 2/422 (0.5) | 5/437 (1.1) |
| Current smoking — no. (%) | 185 (39.0) | 226 (45.7) |
| Hypertension — no. (%) | 178 (37.6) | 183 (37.0) |
| Diabetes mellitus — no. (%) | 65 (13.7) | 58 (11.7) |
| Dyslipidemia — no. (%) | 186 (39.2) | 187 (37.8) |
| Previous myocardial infarction — no. (%) | 28 (5.9) | 26 (5.3) |
| Previous ischemic heart disease — no. (%) | 31 (6.5) | 32 (6.5) |
| Treated with CABG — no./total no. (%) | 1/31 (3.2) | 0/32 |
| Treated with PCI — no./total no. (%) | 26/31 (83.9) | 25/32 (78.1) |
| Managed medically — no./total no. (%) | 4/31 (12.9) | 7/32 (21.9) |
| Previous heart failure — no. (%) | 1 (0.2) | 5 (1.0) |

* Plus-minus values are means ±SD. There were no significant between-group differences in any of the characteristics listed, except for current smoking ($P=0.03$). CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

consistent with those of the modified as-treated (primary) analysis (Table S8 in the Supplementary Appendix). Data for all the outcomes except left ventricular remodeling were available for the entire intention-to-treat population; there were no significant differences between the two groups in these analyses (Table S9 and Fig. S1 in the Supplementary Appendix).

The primary outcome at 1 year was consistent across all the prespecified subgroups except for the analysis stratified according to Killip class at baseline, for which there was a significant interaction between Killip class and treatment effect ($P=0.009$) (Fig. S2 in the Supplementary Appendix). No adverse effects of cyclosporine therapy on renal function, white-cell count, or blood glucose level were detected (Table S10 in the Supplementary Appendix).

DISCUSSION

In patients who had STEMI with anterior infarcts, the intravenous administration of cyclosporine just before PCI did not result in a lower

risk of the composite primary outcome of death from any cause, worsening of heart failure during the initial hospitalization, rehospitalization for heart failure, or adverse left ventricular remodeling than the risk with placebo. Administration of cyclosporine also did not result in a lower risk of any of the individual components of the combined outcome or of any of several secondary outcomes.

Several effect modifiers (e.g., TIMI flow grade at admission, the duration of ischemia, and the timing of drug administration) may attenuate the potential clinical benefit of a treatment that targets reperfusion injury.¹⁷ Coexisting conditions (e.g., diabetes) and concomitant treatments (e.g., antiplatelet therapy) may also influence reperfusion injury and the response to protective interventions.¹⁸ In the CIRCUS trial, however, we found no significant difference in these baseline characteristics (apart from smoking) between the two groups.^{19,20} Hence, the lack of an effect with cyclosporine is unlikely to be related to the influence of any of these effect modifiers or coexisting conditions.

Table 2. Procedural Characteristics.*

| Characteristic | Cyclosporine (N=474) | Control (N=495) |
|--|----------------------|-----------------|
| Time from symptom onset to hospital arrival — hr | 3.4±3.0 | 3.4±3.1 |
| Time from hospital arrival to treatment administration — hr | 1.0±1.3 | 1.1±1.7 |
| Total ischemic time | | |
| Duration — hr† | 4.4±3.0 | 4.5±2.9 |
| Distribution — no./total no. (%) | | |
| <2 hr | 54/432 (12.5) | 42/446 (9.4) |
| 2–6 hr | 306/432 (70.8) | 307/446 (68.8) |
| >6 hr | 72/432 (16.7) | 97/446 (21.7) |
| Prehospital thrombolysis — no./total no. (%) | 28/474 (5.9) | 32/493 (6.5) |
| Medication from first medical care to PCI — no./total no. (%)‡ | | |
| Heparin | 388/474 (81.9) | 408/493 (82.8) |
| Glycoprotein IIb/IIIa inhibitor | 181/474 (38.2) | 185/493 (37.5) |
| Loading dose of P2Y ₁₂ inhibitor | 428/474 (90.3) | 435/493 (88.2) |
| Aspirin | 445/474 (93.9) | 453/493 (91.9) |
| Morphine | 284/474 (59.9) | 270/493 (54.8) |
| Site of occlusion in left anterior descending artery — no. (%) | | |
| Proximal or main left artery | 214 (45.1) | 203 (41.0) |
| Medial or distal segment or diagonal branch | 260 (54.9) | 292 (59.0) |
| Multivessel disease — no. (%) | 194 (40.9) | 164 (33.1) |
| Thrombus burden ≥3 — no./total no. (%) | 311/447 (69.6) | 315/483 (65.2) |
| Rentrop score of 2 or 3 — no./total no. (%)§ | 29/446 (6.5) | 36/483 (7.5) |
| Area at risk — %¶ | 36.5±8.4 | 36.1±8.6 |
| TIMI flow grade before PCI — no./total no. (%) | | |
| 0 | 359/446 (80.5) | 395/483 (81.8) |
| 1 | 55/446 (12.3) | 55/483 (11.4) |
| 2 | 21/446 (4.7) | 27/483 (5.6) |
| 3 | 11/446 (2.5) | 6/483 (1.2) |
| Thrombus aspiration — no. (%) | 359 (75.7) | 377 (76.2) |
| Stenting — no. (%) | 422 (89.0) | 434 (87.7) |
| No reflow observed on angiography — no. (%) | 27 (5.7) | 28 (5.7) |
| TIMI flow grade after PCI — no./total no. (%) | | |
| 0 | 6/466 (1.3) | 7/487 (1.4) |
| 1 | 5/466 (1.1) | 5/487 (1.0) |
| 2 | 33/466 (7.0) | 25/487 (5.1) |
| 3 | 422/466 (90.6) | 450/487 (92.4) |

* Plus–minus values are means ±SD. There were no significant between-group differences in any of the characteristics listed, except for multivessel disease (P=0.01). TIMI denotes Thrombolysis in Myocardial Infarction.

† Data were missing for 42 patients in the cyclosporine group and for 49 in the control group.

‡ Heparin was low-molecular-weight heparin or unfractionated heparin. P2Y₁₂ inhibitors included clopidogrel, prasugrel, and ticagrelor.

§ Scores on the Rentrop classification range from 0 to 3, with higher scores indicating greater degree of collateral circulation. A score of 0 indicates no filling of any collateral channels; 1, filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment; 2, partial filling of the epicardial artery by collateral vessels; and 3, complete filling of the epicardial artery by collateral vessels. Local investigators could not always accurately assess Rentrop scores in emergency settings, so some patients with a Rentrop score of 2 or 3 were included in the trial. This situation was corrected at the end of the trial by the centralized, blinded analysis and was taken into account by the per-protocol analysis.

¶ The area at risk was assessed by means of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) score.¹⁶ The APPROACH score is a scoring system in which the left ventricle is divided into regions defined by the distribution of perfusion of each coronary artery, and the estimated amount of myocardium in each region is used to calculate the amount of jeopardized myocardium for a given site of vessel occlusion. The area at risk is expressed as the percent of the left ventricular mass.

|| Some patients with a TIMI flow grade of 2 or 3 were included by local investigators, which was a protocol deviation. All coronary angiograms were read centrally by persons who were unaware of the study-group assignments, and the situation was taken into account in the per-protocol analysis.

Table 3. Clinical Outcomes at 1 Year in the Modified As-Treated Population.

| Outcome | Cyclosporine (N=395) | Control (N=396) | Odds Ratio (95% CI) | P Value |
|--|-------------------------|--------------------|------------------------|---------|
| | number (percent) | | | |
| Primary composite outcome* | 233 (59.0) | 230 (58.1) | 1.04 (0.78–1.39) | 0.77 |
| Death from any cause | 28 (7.1) | 26 (6.6) | 1.09 (0.63–1.90) | 0.76 |
| Cardiovascular death | 24 (6.1) | 24 (6.1) | 1.01 (0.56–1.81) | 0.98 |
| Heart-failure worsening or rehospitalization for heart failure | 90 (22.8) | 90 (22.7) | 1.01 (0.72–1.41) | 0.97 |
| Heart-failure worsening | 62 (15.7) | 67 (16.9) | 0.92 (0.63–1.34) | 0.65 |
| Rehospitalization for heart failure | 42 (10.6) | 41 (10.4) | 1.03 (0.65–1.63) | 0.89 |
| Left ventricular remodeling | 169 (42.8) | 161 (40.7) | 1.09 (0.82–1.46) | 0.53 |
| Cardiogenic shock | 26 (6.6) | 24 (6.1) | 1.09 (0.61–1.94) | 0.77 |
| Recurrent myocardial infarction | 9 (2.3) | 15 (3.8) | 0.59 (0.26–1.37) | 0.22 |
| Stroke | 7 (1.8) | 12 (3.0) | 0.58 (0.22–1.48) | 0.25 |
| Major bleeding | 7 (1.8) | 9 (2.3) | 0.73 (0.27–2.00) | 0.54 |

* The primary outcome was a composite of death from any cause, worsening of heart failure during the initial hospitalization, rehospitalization for heart failure, or adverse left ventricular remodeling at 1 year.

One important limitation of this trial is that we included in the primary outcome the non-clinical outcome of adverse left ventricular remodeling, which accounted for a substantial proportion of the primary outcome rate. Left ventricular remodeling is a surrogate outcome — one that was not successfully measured in 17.4% of the trial participants. However, in secondary analyses, no beneficial effect of cyclosporine was detected on any of the hard clinical outcomes.

Unlike our previous smaller, phase 2 trial,¹¹ the CIRCUS trial showed no benefit of cyclosporine in reducing the peak release of creatine kinase, a crude estimate of infarct size. This difference may be related to a limited use of direct stenting in the CIRCUS trial or possibly to a higher rate of thrombus aspiration observed in this trial, the inclusion of only patients with anterior infarcts, or a higher rate of use of loading doses of P2Y₁₂ inhibitors, which reduce infarct size.^{11,21} The formulation of cyclosporine may also play a confounding role. In our previous trial, we used Sandimmune (Novartis), whereas in the current trial we used CicloMulsion. The vehicle of Sandimmune (Cremophor EL [polyoxyethylated castor oil]) differs from that of CicloMulsion (lipid emulsion), and both have

been shown to alter mitochondrial respiration and PTP opening in a different manner, possibly influencing infarct size.^{22,23} Whether the vehicles contributed to the discrepancy between the two studies remains to be clarified. However, unpublished data from our group indicate that CicloMulsion is associated with a significant reduction in infarct size in the mouse heart. Previous preclinical and clinical studies evaluating the effects of cyclosporine against reperfusion injury have shown varied results.^{24–31} Cyclosporine is not a specific inhibitor of PTP opening, and its nonmitochondrial effects might have attenuated a potential benefit of inhibition of PTP opening.

Almost one of four patients in the current trial died or was hospitalized for heart failure despite receiving state-of-the-art medical care. This finding is a reminder of the substantial residual risk in this population and the persistent room for improvement in the medical treatment of high-risk patients with STEMI.³² The results of this trial do not challenge the concept that reperfusion injury is clinically important. Recent phase 2 trials that have used either ischemic or pharmacologic postconditioning suggest that interventions applied at the time of reperfusion can limit infarct size and improve functional recovery.^{4,20,33} Their effect on clinical

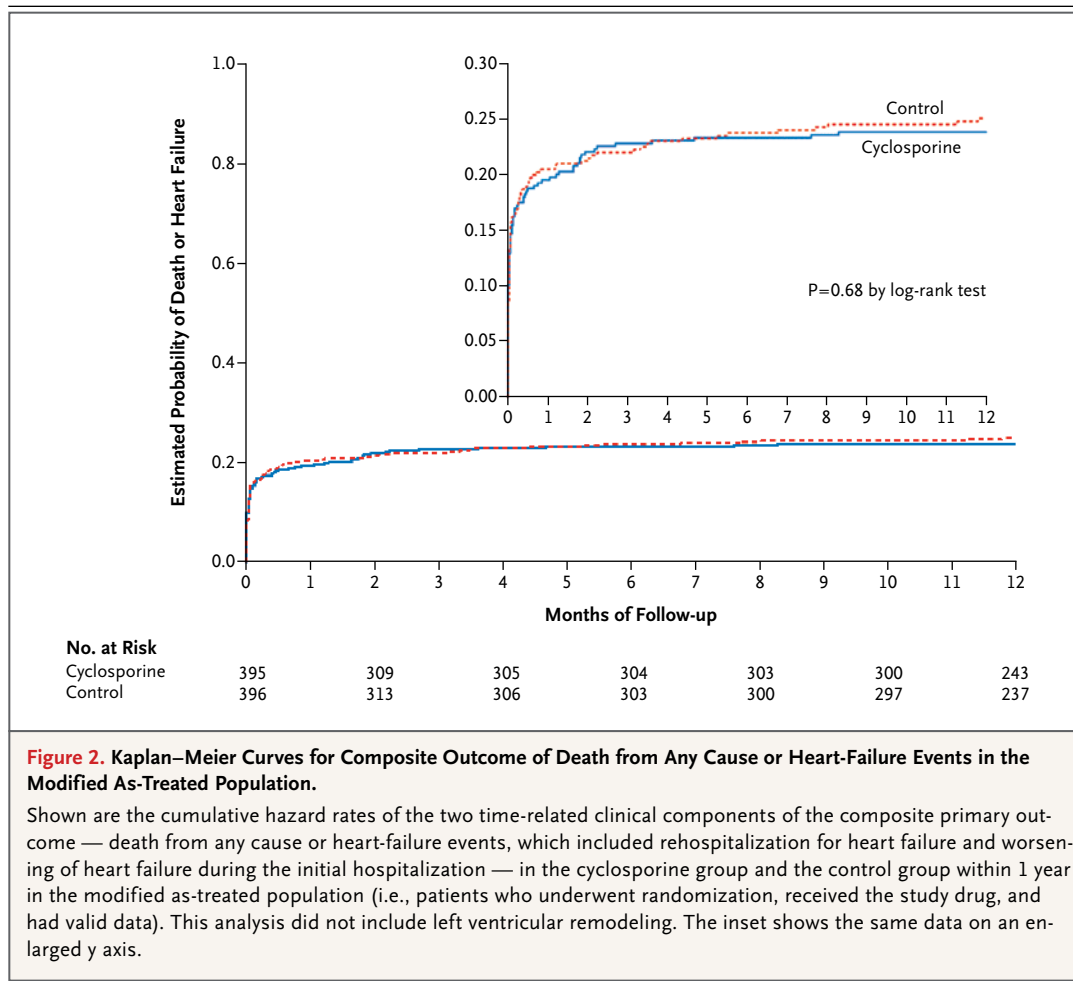


Figure 2. Kaplan–Meier Curves for Composite Outcome of Death from Any Cause or Heart-Failure Events in the Modified As-Treated Population.

Shown are the cumulative hazard rates of the two time-related clinical components of the composite primary outcome — death from any cause or heart-failure events, which included rehospitalization for heart failure and worsening of heart failure during the initial hospitalization — in the cyclosporine group and the control group within 1 year in the modified as-treated population (i.e., patients who underwent randomization, received the study drug, and had valid data). This analysis did not include left ventricular remodeling. The inset shows the same data on an enlarged y axis.

outcome remains to be determined in phase 3 studies.

In conclusion, among patients with anterior STEMI who were referred for primary PCI, we compared the intravenous administration of cyclosporine at a dose of 2.5 mg per kilogram just before PCI with placebo. Cyclosporine did not reduce the risk of the composite outcome of

death from any cause, worsening of heart failure during the initial hospitalization, rehospitalization for heart failure, or adverse left ventricular remodeling at 1 year.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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