ORIGINAL ARTICLE

Apolipoprotein A1 Infusions and Cardiovascular Outcomes after Acute Myocardial Infarction

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CME

ABSTRACT

BACKGROUND

Cardiovascular events frequently recur after acute myocardial infarction, and low cholesterol efflux — a process mediated by apolipoprotein A1, which is the main protein in high-density lipoprotein — has been associated with an increased risk of cardiovascular events. CSL112 is human apolipoprotein A1 derived from plasma that increases cholesterol efflux capacity. Whether infusions of CSL112 can reduce the risk of recurrent cardiovascular events after acute myocardial infarction is unclear.

METHODS

We conducted an international, double-blind, placebo-controlled trial involving patients with acute myocardial infarction, multivessel coronary artery disease, and additional cardiovascular risk factors. Patients were randomly assigned to receive either four weekly infusions of 6 g of CSL112 or matching placebo, with the first infusion administered within 5 days after the first medical contact for the acute myocardial infarction. The primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes from randomization through 90 days of follow-up.

RESULTS

A total of 18,219 patients were included in the trial (9112 in the CSL112 group and 9107 in the placebo group). There was no significant difference between the groups in the risk of a primary end-point event at 90 days of follow-up (439 patients [4.8%] in the CSL112 group vs. 472 patients [5.2%] in the placebo group; hazard ratio, 0.93; 95% confidence interval [CI], 0.81 to 1.05; P=0.24), at 180 days of follow-up (622 patients [6.9%] vs. 683 patients [7.6%]; hazard ratio, 0.91; 95% CI, 0.81 to 1.01), or at 365 days of follow-up (885 patients [9.8%] vs. 944 patients [10.5%]; hazard ratio, 0.93; 95% CI, 0.85 to 1.02). The percentage of patients with adverse events was similar in the two groups; a higher number of hypersensitivity events was reported in the CSL112 group.

CONCLUSIONS

Among patients with acute myocardial infarction, multivessel coronary artery disease, and additional cardiovascular risk factors, four weekly infusions of CSL112 did not result in a lower risk of myocardial infarction, stroke, or death from cardiovascular causes than placebo through 90 days. (Funded by CSL Behring; AEGIS-II ClinicalTrials.gov number, NCT03473223.)

Despite the availability of evidence-based treatments for patients after acute myocardial infarction, including antithrombotic therapy, antiplatelet therapy, lipid-lowering agents, and newer generations of coronary stents, the risk of a recurrent cardiovascular event remains substantial,[1,2] particularly in the initial 90-day period after the acute myocardial infarction.[3] The presence of multivessel coronary artery disease, diabetes, and other established risk factors is known to exacerbate this risk.[4,5] Thus, given that current secondary preventive therapies do not adequately address this residual risk, new therapeutic approaches are needed.

The disruption of atherosclerotic plaque that consists of lipid-laden macrophages and a necrotic core is commonly the primary pathophysiological event in acute myocardial infarction.[6] Reverse cholesterol transport is the mechanism by which excess cholesterol, such as atherosclerotic plaque, is removed from peripheral tissues and transported to the liver for excretion in the bile. The initial step in reverse cholesterol transport involves cholesterol efflux, which is mediated predominantly by apolipoprotein A1, the main protein in high-density lipoproteins (HDLs).[7] Patients with acute coronary syndromes have an impaired cholesterol efflux capacity,[8] which has been independently associated with a higher incidence of major adverse cardiovascular events,[9] including a higher incidence of both short-term (30-day) and long-term death from any cause in patients who have had an acute myocardial infarction event.[10]

CSL112 is human plasma–derived apolipoprotein A1 that is formulated with phosphatidylcholine to form disk-shaped particles that are suitable for intravenous infusion. In previous studies, a 6-g dose of CSL112 resulted in immediate and robust increases in apolipoprotein A1 levels (to twice the baseline level) and cholesterol efflux capacity (to four times that of baseline). A dosing regimen of four weekly infusions was chosen to maximize exposure but minimize accumulation in a logistically practical way during the weeks after acute myocardial infarction.[11-15] We hypothesized that CSL112 administered weekly for 4 weeks beginning immediately after the occurrence of acute myocardial infarction would reduce the risk of myocardial infarction, stroke, and death from cardiovascular causes during the 90-day high-risk period after acute myocardial infarction.

METHODS

STUDY OVERSIGHT

AEGIS-II (ApoA-I Event Reducing in Ischemic Syndromes II) was an international, double-blind, randomized, placebo-controlled trial. Details of the trial design have been published previously.[16] The executive committee and the trial sponsor, CSL Behring, were responsible for the design and oversight of the trial. The manuscript was prepared by the first author with input from all the authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). Statistical analyses were independently performed by the PERFUSE Study Group statistician. The study was approved by national regulatory agencies and by the institutional review board or ethics committee at each participating site, and all patients who were included in the analysis provided written informed consent. An independent data monitoring committee monitored the scientific integrity and the safety of the patients in the trial, and the Cleveland Clinic Coordinating Center for Clinical Research led the blinded, independent end-point adjudication (members are listed in the Supplementary Appendix, available at NEJM.org).

A Quick Take is available at NEJM.org

STUDY POPULATION

Patients were eligible for enrollment if they were at least 18 years of age and had had a type 1 (spontaneous) myocardial infarction as defined according to the fourth universal definition of myocardial infarction.[17] In addition, patients were required to have multivessel coronary artery disease and evidence of additional cardiovascular risk. Initially, patients were required to have one of the following risk factors: pharmacologic treatment for diabetes, an age of 65 years or older, a history of myocardial infarction, or peripheral artery disease. After a protocol amendment was implemented within the first year after the start of the trial, this criterion was revised to require either pharmacologic treatment for diabetes or two or more of the other risk factors noted above.

Key exclusion criteria were evidence of hepatobiliary disease, ongoing hemodynamic instability, left ventricular ejection fraction of less than 30%, an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area, scheduled coronary-artery bypass graft surgery as a treatment for the index myocardial infarction, or a body weight of less than 50 kg. A full list and description of the inclusion and exclusion criteria can be found in the Supplementary Appendix.

Randomization was stratified according to the type of index myocardial infarction (ST-segment elevation myocardial infarction [STEMI] vs. non-STEMI [NSTEMI]), management of the index myocardial infarction (percutaneous coronary intervention [PCI] vs. medical management), and geographic region (North America, Latin America, Western Europe, Central and Eastern Europe, or Asia Pacific). Patients were then randomly assigned, in a 1:1 ratio, to receive either 6 g of CSL112 or matching placebo (4.4% albumin solution), both of which were infused intravenously over 2 hours. The first infusion of CSL112 or placebo was administered at least 12 hours after the patient's presentation with acute myocardial infarction or at least 12 hours after the administration of intravenous contrast medium if used for cardiac catheterization, whichever came later, and within 5 days after the first medical contact for the index acute myocardial infarction. Patients received intravenous infusions of CSL112 or placebo once a week for four consecutive weeks; infusions were administered approximately 7 days (minimum of 5 days) apart and within 30 days after randomization. Patients were assessed at screening; at each infusion visit; at days 29, 60, and 90; and then every 90 days until the final visit at day 365.

ANALYSIS POPULATIONS

Efficacy analyses were performed according to the intention-to-treat principle and included data from all patients who underwent randomization, regardless of whether they received CSL112 or placebo. Safety analyses were based on the trial product (CSL112 or placebo) that the patients actually received and included all patients who underwent randomization and received at least one dose of CSL112 or placebo.

END POINTS

The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes from the time of randomization through 90 days, assessed in a time-to-first-event analysis. Key secondary efficacy end points included the total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days and a composite of myocardial infarction, stroke, or death from cardiovascular causes from the time of randomization through 180 days and through 365 days, assessed in a time-to-first-event analysis.

Other secondary efficacy end points included each component of the primary efficacy composite end point (myocardial infarction, stroke, and death from cardiovascular causes) from the time of randomization through 90 days, as well as death from any cause from the time of randomization through 365 days — all assessed in time-to-first-event analyses. All primary and secondary end points were adjudicated by the members of the independent adjudication committee, who were unaware of the treatment assignments. Other secondary end points that were used to assess safety included the number of patients with adverse events that occurred from the beginning of the treatment period through 90 days and the number of patients with serious adverse events that occurred from the beginning of the treatment period through the end of the trial.

STATISTICAL ANALYSIS

We initially calculated that with 1004 primary end-point events, the trial would have a power of more than 90% on the basis of an assumed hazard ratio of 0.80 for the primary end point and an estimated percentage of patients with an event in the placebo group of 6.4%, at a two-sided type I error rate of 0.05; this calculation resulted in a target sample size of 17,400 patients. After a prespecified reestimation on the basis of 5% of patients with an event at 75% of the planned enrollment, the final target sample size was adjusted to approximately 18,200, targeting 905 primary end-point events, which maintained the 90% power.

Cumulative event rates were calculated with the use of the Kaplan–Meier method for the

primary efficacy end point and for the other time-to-event end points. A covariate-adjusted Cox regression model that included fixed effects for regimen, region, index myocardial infarction type, index myocardial infarction management, age, the presence of diabetes, the presence of peripheral artery disease, previous myocardial infarction, and an interaction term for index myocardial infarction type and index myocardial infarction management was fitted to estimate the hazard ratio and two-sided 95% confidence interval, as well as a two-sided P value (with a P value of less than 0.05 considered to indicate significance). The proportional hazards assumption was assessed graphically with the use of a plot of the log cumulative hazard. A negative binomial regression model with a log-link function that included the same covariates as the Cox regression model was used to analyze the key secondary end point of hospitalizations for ischemic events. The statistical analysis plan specified one-sided hypothesis testing and P values, but two-sided P values are reported here in line with the *Journal*'s policy.

Multiplicity in testing the primary and key secondary end points was addressed with the use of a serial gatekeeping procedure for three prespecified families of null hypotheses to control the overall type I error rate at a two-sided level of 0.05. If significance was not achieved at any step in the procedure, any remaining secondary outcomes were considered to be exploratory. Additional details on the statistical methods related to hierarchical testing can be found in the Supplementary Appendix. An independent data monitoring committee performed prespecified interim analyses to assess futility after approximately 30% and 50% of the targeted number of primary end-point events had accrued and performed an interim analysis to assess efficacy after 70% of the target events had accrued. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

A total of 18,848 patients provided informed consent and underwent screening. Of these, 18,226 patients at 886 sites in 49 countries underwent randomization from March 2018 through November 2022. After the exclusion of 7 patients because of concerns with respect to the quality of the data at one site, 18,219 patients were included in the intention-to-treat analysis; 9112 were randomly assigned to receive CSL112 and 9107 were randomly assigned to receive placebo (Fig. S1 in the Supplementary Appendix).

The baseline characteristics were well balanced between the two treatment groups (Table 1). The mean age of the patients was 65.5 years, and 74.1% (13,507 patients) were men. The representativeness of patients enrolled in the trial with respect to age, sex, and geographic region is shown in Table S1. The percentage of patients with a qualifying STEMI was similar to the percentage with an NSTEMI. Patients were receiving appropriate treatment with guideline-recommended medications, including dual antiplatelet therapy and 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins), and the majority (88.0%) had undergone PCI for the index event (Table 1).

The final patient completed the trial on November 17, 2023. Most patients attended the follow-up visit at 90 days (99.4% [18,101 patients]) and at 365 days (98.9% [18,022 patients]), with no differences between treatment groups in the reasons for not completing the study. The percentage of patients who underwent randomization but did not receive CSL112 or placebo was 1.2% in the CSL112 group (105 patients) and 0.8% in the placebo group (77 patients). All four infusions were received by 89.8% of patients in the CSL112 group (8187 of 9112 patients) and by 90.0% of patients in the placebo group (8192 of 9107). The percentage of patients who discontinued the trial regimen was 8.4% in the CSL112 group (766 patients) and 8.5% in the placebo group (775 patients); the primary reasons for discontinuation were patient decision, nonfatal adverse events, death, and other (e.g., logistic reasons). A summary of the infusions that were received is provided in Table S2. The primary end point was ascertained for 99.4% of the potential patient-years of follow-up, and vital status was ascertained for 99.5% of the 18,219 patients who were included in the intention-to-treat analysis. The percentage of patients who withdrew consent to participate in the trial was 0.5% in

Table 1. Baseline Characteristics of the Patients.*

Characteristic	CSL112 (N=9112)	Placebo (N=9107)
Age		
Mean — yr	65.6±10.1	65.4±10.2
≥65 yr — no. (%)	5418 (59.5)	5341 (58.6)
Male sex — no. (%)	6786 (74.5)	6721 (73.8)
Race or ethnic group — no. (%)†		
White	7769 (85.3)	7698 (84.5)
Asian	743 (8.2)	781 (8.6)
Black	181 (2.0)	181 (2.0)
Other	373 (4.1)	402 (4.4)
Hispanic or Latino	1566 (17.2)	1596 (17.5)
Geographic region — no. (%)		
Western Europe	2459 (27.0)	2455 (27.0)
Central and eastern Europe	3134 (34.4)	3136 (34.4)
Latin America	1456 (16.0)	1453 (16.0)
North America	1178 (12.9)	1175 (12.9)
Asia Pacific	885 (9.7)	888 (9.8)
Body-mass index‡	29.02±4.99	29.08±5.16
Current smoker — no. (%)	2367 (26.0)	2378 (26.1)
Medical history — no. (%)		
Diabetes requiring pharmacotherapy	6280 (68.9)	6246 (68.6)
Peripheral artery disease	1140 (12.5)	1161 (12.7)
Previous myocardial infarction	3325 (36.5)	3353 (36.8)
Previous coronary revascularization	3504 (38.5)	3500 (38.4)
Heart failure	896 (9.8)	951 (10.4)
Ischemic stroke	468 (5.1)	491 (5.4)
Hypertension	7263 (79.7)	7210 (79.2)
Hypercholesterolemia	5839 (64.1)	5781 (63.5)
Type of index myocardial infarction — no. (%)		
STEMI	4606 (50.5)	4600 (50.5)
NSTEMI	4506 (49.5)	4507 (49.5)
Procedure performed for index myocardial infarction — no. (%)		
Coronary angiography	8869 (97.3)	8868 (97.4)
Percutaneous coronary intervention	8037 (88.2)	7997 (87.8)

Table 1. (Continued.)

Characteristic	CSL112 (N=9112)	Placebo (N=9107)
Medications at randomization — no. (%)		
Aspirin	8489 (93.2)	8473 (93.0)
P2Y12 inhibitor or other antiplatelet agent	8508 (93.4)	8490 (93.2)
HMG-CoA reductase inhibitor, a statin	8429 (92.5)	8424 (92.5)
High-intensity statin therapy§	6871 (75.4)	6890 (75.7)
Median lipid value (IQR) — mg/dl¶		
Total cholesterol	160 (133–192)	159 (133–190)
LDL cholesterol	84 (61–112)	84 (62–111)
HDL cholesterol	39 (33–46)	39 (33–47)
Triglycerides	156 (117–212)	153 (117–208)
Renal function — no. (%)‖		
Normal, eGFR ≥90 ml/min/1.73 m^2	2260 (24.8)	2256 (24.8)
Mild impairment, eGFR ≥60 to <90 ml/min/1.73 m^2	4496 (49.3)	4436 (48.7)
Moderate impairment, eGFR ≥30 to <60 ml/min/1.73 m^2	2017 (22.1)	2134 (23.4)
Severe impairment, eGFR <30 ml/min/1.73 m^2	60 (0.7)	45 (0.5)

* Plus–minus values are means ±SD. HMG-CoA denotes 3-hydroxy-3-methylglutaryl–coenzyme A, IQR interquartile range, NSTEMI non–ST-segment elevation myocardial infarction, STEMI ST-segment elevation myocardial infarction.
† Race and ethnic group were reported by the patients. Race was not reported for 46 patients (0.5%) in the CSL112 group and 45 patients (0.5%) in the placebo group. The category "other" includes patients who reported their race as American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or other, which includes multiple races. Information on whether patients identified as Hispanic or Latino was not reported for 132 patients (1.4%) in the CSL112 group and 123 patients (1.4%) in the placebo group. Additional details about race and ethnicity are provided in Table S1.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Information on high-intensity statin therapy was derived on the basis of the reported use of atorvastatin at a dose of 40 mg or more daily or rosuvastatin at a dose of 20 mg or more daily.
¶ To convert the values for high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.
‖ The values shown for estimated glomerular filtration rate (eGFR) are baseline central laboratory values. A total of 279 patients in the CSL112 group (3.1%) and 236 patients in the placebo group (2.6%) were missing a baseline central laboratory assessment of eGFR. Renal function eligibility was determined by local laboratory values, for which there were no missing values.

the CSL112 group (47 patients) and 0.5% in the placebo group (42 patients). One patient in each treatment group was lost to follow-up at the end of the trial (Fig. S1).

MAJOR CARDIOVASCULAR ADVERSE EVENTS

There was no significant difference between the two groups in the risk of myocardial infarction, stroke, or death from cardiovascular causes from randomization through 90 days (439 patients [4.8%] in the CSL112 group vs. 472 patients [5.2%] in the placebo group had a first event; hazard ratio, 0.93; 95% confidence interval [CI], 0.81 to 1.05; P=0.24) (Fig. 1 and Table 2). The results were consistent across multiple subgroups (Fig. S2). The cumulative incidence of each of the individual components of the primary end point is shown in Figure 1 and in Table 2. The CSL112

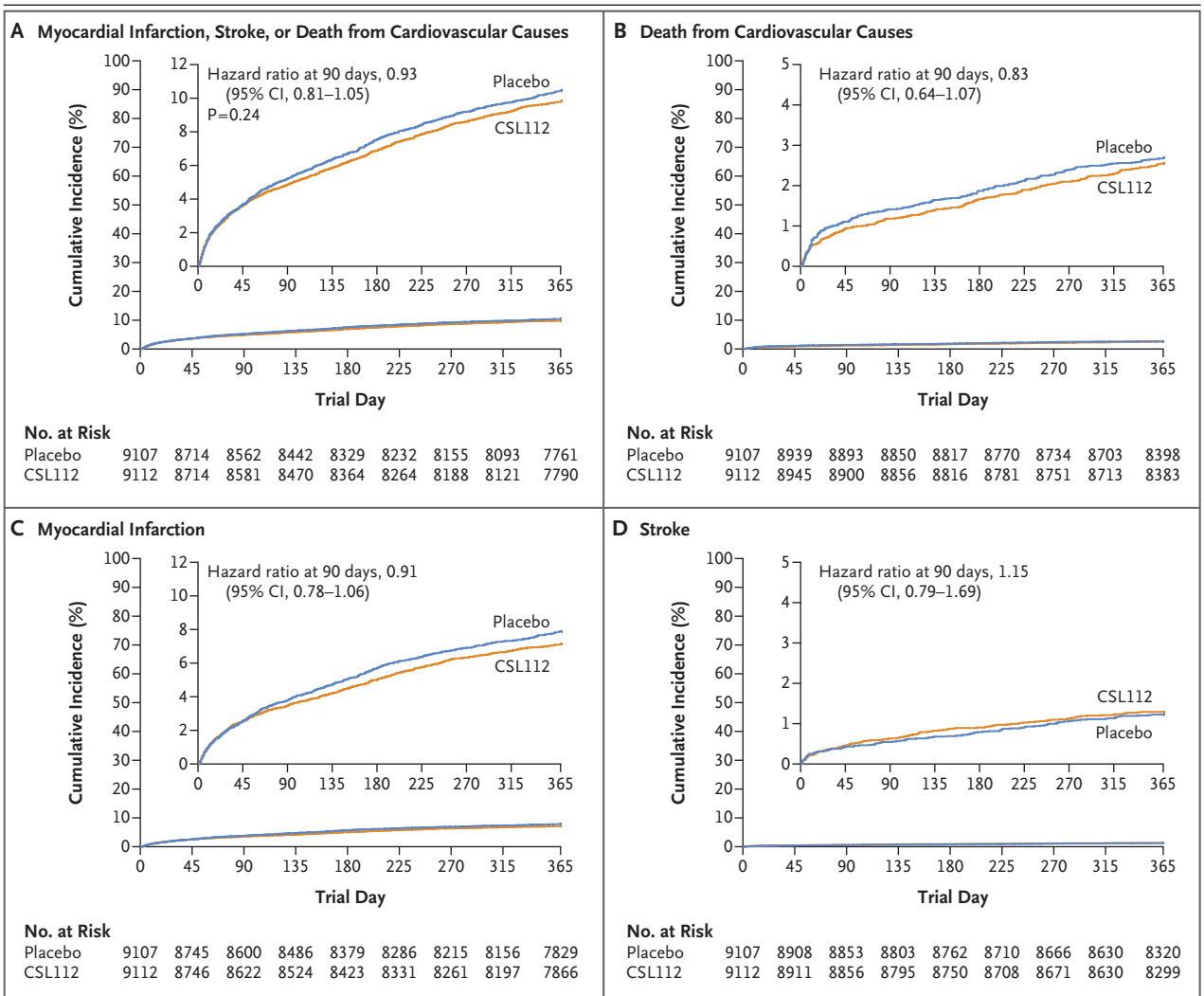

Figure 1. Primary Efficacy End Point and Individual Components of the Primary End Point.

Panel A shows the cumulative incidence of a composite of myocardial infarction, stroke, or death from cardiovascular causes through 90 days (primary end point) and through 180 and 365 days (key secondary end points). Panels B, C, and D show the cumulative incidence of the individual components of the composite end point through 365 days. All assessments were performed in a time-to-first-event analysis. The insets show the data on an enlarged y axis.

group had a lower number of myocardial infarctions and deaths from cardiovascular causes and a higher number of strokes than the placebo group. The majority of strokes were ischemic (at 90 days there were 53 events in the CSL112 group vs. 46 events in the placebo group), although the specific etiologic subtypes (e.g., large-artery atherosclerosis, cardioembolic, small-artery occlusion, or other) were not determined. The remainder of the strokes were classified as hemorrhagic (4 events vs. 2 events) or undetermined type (0 events vs. 1 event).

Superiority testing for the key secondary end points was not performed because the between-group difference in the primary end point did not meet statistical significance. The mean rate of hospitalization for coronary, cerebral, or peripheral ischemia at 90 days was similar in the CSL112 and placebo groups (0.045 vs. 0.047; rate ratio, 0.97; 95% CI, 0.84 to 1.12). The percentage

Table 2. Primary and Secondary Efficacy End Points.*

End Point	CSL112 (N=9112)	Placebo (N=9107)	Hazard Ratio (95% CI)
Primary end point — no. of patients (%)			
Composite of myocardial infarction, stroke, or death from cardiovascular causes through 90 days†	439 (4.8)	472 (5.2)	0.93 (0.81–1.05)
Myocardial infarction through 90 days	312 (3.5)	342 (3.8)	0.91 (0.78–1.06)
Stroke through 90 days	57 (0.6)	49 (0.5)	1.15 (0.79–1.69)
Death from cardiovascular causes through 90 days	107 (1.2)	128 (1.4)	0.83 (0.64–1.07)
Key secondary efficacy end points			
No. of hospitalizations for coronary, cerebral, or peripheral ischemia at 90 days (mean rate over 90 days)	433 (0.045)	442 (0.047)	0.97 (0.84–1.12)‡
Composite of myocardial infarction, stroke, or death from cardiovascular causes through 180 days — no. of patients (%)	622 (6.9)	683 (7.6)	0.91 (0.81–1.01)
Myocardial infarction, stroke, or death from cardiovascular causes through 365 days — no. of patients (%)	885 (9.8)	944 (10.5)	0.93 (0.85–1.02)
Other secondary efficacy end points — no. of patients (%)			
Death from any cause at 365 days	341 (3.8)	345 (3.8)	0.98 (0.84–1.14)
Myocardial infarction through 180 days	450 (5.0)	513 (5.7)	0.87 (0.77–0.99)
Myocardial infarction through 365 days	638 (7.2)	705 (7.9)	0.90 (0.81–1.00)
Stroke through 180 days	81 (0.9)	71 (0.8)	1.13 (0.82–1.56)
Stroke through 365 days	115 (1.3)	109 (1.2)	1.05 (0.89–1.36)
Death from cardiovascular causes through 180 days	150 (1.7)	169 (1.9)	0.88 (0.71–1.10)
Death from cardiovascular causes through 365 days	230 (2.6)	242 (2.7)	0.94 (0.79–1.13)

* All end points except for hospitalization for coronary, cerebral, or peripheral ischemia were assessed in a time-to-first-event analysis. Percentages are the Kaplan–Meier estimates.
† P=0.24 for the comparison between the groups. In accordance with the hierarchical testing procedure, no P values are provided for the other end points because superiority testing for the between-group difference in the primary end point did not meet statistical significance.
‡ This value is a rate ratio rather than a hazard ratio.

of patients with a first occurrence of myocardial infarction, stroke, or death from cardiovascular causes (Kaplan–Meier estimate) was not significantly lower in the CSL112 group than in the placebo group at 180 days (622 patients [6.9%] vs. 683 patients [7.6%]; hazard ratio, 0.91; 95% CI, 0.81 to 1.01) or at 365 days of follow-up (885 patients [9.8%] vs. 944 patients [10.5%]; hazard ratio, 0.93; 95% CI, 0.85 to 1.02). Lipid variables were similar in the treatment groups at baseline and at the end of the infusion period (day 29) (Table S3).

SAFETY OUTCOMES

Overall, a similar percentage of patients in the CSL112 group and the placebo group had adverse events (Table 3). The number of patients with immune system disorders (e.g., hypersensitivity or anaphylactoid reactions) that resulted in discontinuation of the investigational regimen

Table 3. Investigator-Reported Adverse Events.*

Event	CSL112 (N = 9010)	Placebo (N = 9027)	P Value†
	no. of patients (%)		
Any adverse event from the beginning of the treatment period through 90 days	3938 (43.7)	3927 (43.5)	0.79
Serious adverse events	1514 (16.8)	1557 (17.2)	0.43
Cardiac disorders	513 (5.7)	514 (5.7)	1.00
Infections and infestations	394 (4.4)	401 (4.4)	0.83
Gastrointestinal disorders	168 (1.9)	176 (1.9)	0.70
Renal and urinary disorders	151 (1.7)	138 (1.5)	0.44
Respiratory, thoracic, and mediastinal disorders	116 (1.3)	120 (1.3)	0.84
Nonfatal adverse events leading to permanent discontinuation of the investigational product, irrespective of seriousness	221 (2.5)	214 (2.4)	0.73
Renal and urinary disorders	39 (0.4)	51 (0.6)	0.24
Infections and infestations	35 (0.4)	33 (0.4)	0.81
Skin and subcutaneous tissue disorders	31 (0.3)	24 (0.3)	0.35
Investigations	29 (0.3)	19 (0.2)	0.15
Immune-system disorders	14 (0.2)	4 (<0.1)	0.02
Prespecified adverse events of special interest, irrespective of seriousness			
Hypersensitivity‡	214 (2.4)	206 (2.3)	0.69
Serious hypersensitivity events‡	17 (0.2)	15 (0.2)	0.73
Acute kidney injury§	570 (6.3)	650 (7.2)	0.02
Potential hepatic injury¶	39 (0.4)	25 (0.3)	0.08
New or worsening heart failure‖	281 (3.1)	262 (2.9)	0.41

* Per protocol, all adverse events were to be reported through trial day 90, after which all serious adverse events, events resulting in discontinuation of the investigational product, events considered by the investigator to be related to the investigational product, and events leading to withdrawal from the trial were to be reported.
† P values are two-sided and were calculated with Fisher's exact test for the test of no difference.
‡ Hypersensitivity events were defined by the *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.1, Standard MedDRA Queries Hypersensitivity (narrow).
§ Acute kidney injury is defined as any increase in serum creatinine level of 0.3 mg per deciliter (26.5 μmol per liter) or more from the baseline serum creatinine level during the active treatment period.
¶ Potential hepatic injury was defined as any occurrence of either concomitant elevations in alanine aminotransferase level of more than 3 times the upper limit of the normal range with a total bilirubin level of more than 2 times the upper limit of the normal range or an alanine aminotransferase level of more than 5 times the upper limit of the normal range.
‖ New or worsening heart-failure events were adjudicated by the members of the clinical events committee, who were unaware of the treatment assignments.

was low but was higher in the CSL112 group than in the placebo group (14 patients vs. 4 patients; P=0.02). A smaller percentage of patients in the CSL112 group than in the placebo group had acute kidney injury events, defined by increases in creatinine of 0.3 mg per deciliter (26.5 μmol per liter) or more from baseline during the active treatment period (570 of 9010 patients [6.3%] vs. 650 of 9027 patients [7.2%]; P=0.02).

DISCUSSION

Among patients with acute myocardial infarction and multivessel coronary artery disease who had additional cardiovascular risk factors, four weekly infusions of CSL112 did not result in a lower risk of myocardial infarction, stroke, or death from cardiovascular causes through 90 days than placebo. The efficacy results were consistent across the prespecified subgroups. Overall, a similar percentage of patients in the CSL112 group and the placebo group had adverse events. The number of patients who had hypersensitivity or anaphylactic reactions that resulted in discontinuation of the investigational product was very low, which is consistent with other plasma-derived protein therapies, but the number was higher in the CSL112 group than in the placebo group.

A major scientific question that this trial attempted to investigate is whether enhancing HDL function can protect against atherosclerotic disease (the HDL hypothesis). Our clinical outcomes trial directly tested whether modulating HDL function by enhancing cholesterol efflux capacity with CSL112, as opposed to attempting to increase HDL cholesterol levels, would lead to reductions in major adverse cardiovascular events. On the basis of animal and human data that showed favorable remodeling of atherosclerotic plaque after infusions of apolipoprotein A1,[18-20] our prespecified hypothesis was that administering these infusions after a myocardial infarction would stabilize atherosclerotic plaque and lead to a reduction in the risk of major adverse cardiovascular events. Furthermore, impaired cholesterol efflux capacity has been associated with poorer outcomes after a myocardial infarction,[10] and CSL112 has been shown previously to improve cholesterol efflux capacity in the post–myocardial infarction context.[13] Although there was no reduction in the incidence of the primary composite end point, a positive trend was seen with respect to the individual component of myocardial infarction (i.e., fewer events in the CSL112 group than in the placebo group) that could be consistent with the proposed biologic effect. There was a gradual separation of the curves (Fig. 1), with a maximal difference in myocardial infarction between the two treatment groups at 6 months, which could be consistent with remodeling and subsequent stabilization of atherosclerotic plaque.

Testing the HDL hypothesis in the context of successful implementation of low-density lipoprotein–lowering therapies is increasingly challenging. The patients in this trial showed excellent adherence to evidence-based and guideline-directed therapies that also included dual antiplatelet therapy. If apolipoprotein A1 infusions have a benefit in reducing myocardial infarction beyond that of modern pharmacotherapies and device-based therapies, the benefit appears to be modest. Also unclear is whether the treatment effect would have been different with other treatment regimens (e.g., starting infusions before the primary PCI or treating for a longer duration) or in other patient populations, such as patients without acute myocardial infarction.

This trial has certain limitations. It was conducted during the global coronavirus disease 2019 pandemic, which may have influenced results; however, an exploratory analysis showed similar results with respect to the primary end point before and after a temporary pause in enrollment during the early weeks of the pandemic (data not shown here). Approximately 0.5% of patients withdrew their consent during the trial, and we were unable to ascertain the vital status in most of those patients because of updated privacy laws. The representation of women and certain racial minority groups was low and could impact the overall generalizability of the findings.

This trial showed that among patients with acute myocardial infarction, multivessel coronary artery disease, and additional cardiovascular risk factors who were receiving guideline-directed background therapies, the risk of

myocardial infarction, stroke, or death from cardiovascular causes through 90 days was not lower with four weekly infusions of CSL112 than with placebo.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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