Effects of pyridoxal-5'-phosphate (MC-1) in patients undergoing high-risk coronary artery bypass surgery: Results of the MEND-CABG randomized study

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Supplemental material is available online

Objective: Coronary artery bypass graft surgery remains associated with significant postoperative cardiovascular morbidity and mortality in high-risk patients. MC-1 (pyridoxal-5'-phosphate monohydrate) inhibits purinergic receptors and intracellular influx of Ca^{2+} , thereby reducing cellular injury during experimental ischemia and reperfusion. The MEND-CABG trial tested the hypothesis that MC-1 reduces cardiovascular morbidity and mortality after coronary artery bypass graft.

Methods: In a phase 2, double-blinded, placebo-controlled study, 901 patients scheduled for coronary artery bypass graft surgery with cardiopulmonary bypass and at high risk for subsequent cardiac or neurologic complications were randomly assigned to receive oral MC-1 (250 mg or 750 mg/d once daily) or placebo beginning 3 to 10 hours prior to surgery and continued to postoperative day 30.

Results: At 30 days, MC-1 250 mg (compared with placebo) reduced the composite of death, nonfatal cerebral infarction, and nonfatal myocardial infarction by 14.0% ($P = .3124$) with peak creatinine kinase-myocardial band ≥ 50 ng/mL (prespecified primary end point); 32.3% ($P = .0349$) with peak creatinine kinase-myocardial band ≥ 70 ng/mL; and 37.2% ($P = .0283$) with peak creatinine kinase-myocardial band ≥ 100 ng/mL. Myocardial infarctions with peak creatinine kinase-myocardial band ≥ 100 ng/mL were reduced by 47.2% in the MC-1 250-mg group versus placebo ($P = .0083$). Greater efficacy was demonstrated with 250 mg than with the 750-mg dose of MC-1.

Conclusions: In high-risk patients undergoing coronary artery bypass graft, treatment with MC-1 did not significantly affect the prespecified primary end point but was associated with a significant reduction in perioperative myocardial infarction with creatinine kinase-myocardial band ≥ 100 ng/mL. A larger, well-powered trial is needed to evaluate the cardioprotective effects of MC-1.

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Coronary artery bypass graft (CABG) surgery effectively relieves angina and results in longer survival in specific subgroups of patients with complex coronary disease and left ventricular dysfunction.¹⁻³ Due to the high incidence of coronary artery disease worldwide, as well as the effectiveness of this surgical procedure, CABG surgery makes up 1 of the top 10 most frequently performed procedures in North America and Europe.^{4,5} Despite the benefits of CABG surgery, the procedure is associated with a risk of perioperative mortality, myocardial infarction, unstable angina, heart failure, life-threatening arrhythmia, renal insufficiency, and stroke, often due to episodes of ischemia and reperfusion.⁶⁻¹⁰ The impact of these complications is significant with incidence rates of death and major cardiovascular and cerebrovascular events following CABG surgery of up to 20% depending on the patient's risk profile and diagnostic criteria.¹¹⁻¹⁶

Abbreviations and Acronyms

ATP	= adenosine triphosphate
CABG	= coronary artery bypass graft
CEC	= Clinical Endpoint Committee
CK-MB	= creatinine kinase–myocardial band
ECG	= electrocardiogram
MI	= myocardial infarction
P-5'-P	= pyridoxal-5'-phosphate monohydrate
PCI	= percutaneous coronary intervention
POD	= postoperative day

Although advances in surgical techniques, anesthetic management, and postoperative care have resulted in a steady decline in post-CABG morbidity and mortality during the past 2 decades,^{17,18} there clearly remains a need to reduce the number of complications associated with cardiac surgery. Considering the substantial number of patients who undergo CABG every year along with the incidence of sequelae, cardioprotection and neuroprotection represent significant unmet medical needs.

MC-1 is an investigational drug that contains pyridoxal-5'-phosphate monohydrate (P-5'-P). P-5'-P is a naturally occurring metabolite of pyridoxine and is formed in mammalian cells by phosphorylation and oxidation reactions. MC-1 is a purinergic (P2) receptor antagonist that blocks intracellular influx of Ca^{2+} , thereby reducing cell damage during experimental episodes of ischemia and reperfusion.¹⁹ A phase 2 dose-ranging, single-blinded study (MEND-1) evaluated the effects of 10 mg/kg/d MC-1 given for up to 14 days in patients at high risk for ischemic complications during percutaneous coronary intervention (PCI).²⁰ Results demonstrated a decrease in infarct size over the first 24 hours following PCI, suggesting the cardioprotective properties of MC-1 in the setting of ischemia and reperfusion. The MC-1 to Eliminate Necrosis and Damage in CABG (MEND-CABG) trial was a phase 2 study that intended to evaluate the potential cardio- and neuroprotective effects of MC-1 in patients undergoing CABG with cardiopulmonary bypass and considered at high risk for perioperative vascular events.

Materials and Methods**Study Design and Patient Selection**

Following approval by individual Ethics Committees and Institutional Review Boards, enrollment for the double-blinded, placebo-controlled MEND-CABG trial was conducted at 40 centers in Canada and the United States (Appendix E1) between April 2004 and July 2005. Patients eligible for the study were those scheduled for CABG surgery with cardiopulmonary bypass but without associated valve surgery who were considered at high risk for perioperative cardio- and/or cerebrovascular complications according to 2 or more of the following criteria: age >65 years;

current smoker; history of diabetes mellitus requiring treatment other than diet; history of nondisabling stroke, transient ischemic attack, or carotid endarterectomy; prior peripheral artery surgery or angioplasty; recent myocardial infarction (MI) (≥ 48 hours and ≤ 6 weeks before surgery); evidence of left ventricular dysfunction or congestive heart failure; need for urgent CABG; renal dysfunction with serum creatinine between 133 and $<250 \mu\text{mol/L}$ (1.5–2.8 mg/dL); or presence of stenosis ($\geq 50\%$) in ≥ 1 carotid artery. Patients with planned associated valve surgery, concurrent carotid endarterectomy, aortic dissection repair, aortic root reconstruction, or surgery for atrial fibrillation were excluded, as were patients with current cardiogenic shock, left ventricular rupture, ventricular septal rupture, papillary muscle rupture, uncontrolled diabetes [fasting plasma glucose $\geq 24 \text{ mmol/L}$ (432 mg/dL)], creatinine $\geq 250 \mu\text{mol/L}$ (2.8 mg/dL), liver cirrhosis, chronic active hepatitis, severe liver dysfunction, MI occurring <48 hours prior to planned CABG surgery, history of malignancy during the last 5 years, potential for pregnancy, or history of alcohol or drug abuse within the past year. Finally, patients who could not be screened at least 4 hours before the scheduled CABG were excluded.

After written informed consent was obtained, patients were randomly assigned in a 1:1:1 ratio (using an interactive voice response system) to receive MC-1 250 mg, MC-1 750 mg, or matching placebo tablets administered orally once daily. The first dose of study medication was administered 3 to 10 hours prior to CABG surgery and treatment continued for 30 days after surgery. During CABG surgery, the use of cardiopulmonary bypass, moderate systemic hypothermia (34°C), and routine anticoagulation were required per protocol. Patients unable to swallow pills postoperatively were allowed to receive study medication through a nasogastric tube. During the 90-day postoperative period, patient observations were carried out through 72 hours, at postoperative day (POD) 4, at discharge, at POD 30, and at POD 90.

Study End Points and Definitions

The primary efficacy end point was the difference between treatment groups in the combined incidence of cardiovascular death, nonfatal MI, and nonfatal cerebral infarction up to and including POD 30. Secondary efficacy end points included individual components of the combined end point, area under the curve of creatinine kinase–myocardial band (CK-MB) within the first 24 hours post-CABG, all-cause mortality, and composite and component end points up to POD 90. An independent Clinical Endpoint Committee (CEC) composed of cardiologists and neurologists experienced in patient care reviewed all potential episodes of the primary end point components, and their determination was used in the final analysis. Each reported death, stroke, and MI was classified according to predetermined guidelines. All deaths without an identifiable noncardiovascular cause were attributed to a cardiovascular cause. Myocardial infarction was defined based on central laboratory or core electrocardiogram (ECG) laboratory data as follows: (1) a peak CK-MB value $\geq 50 \text{ ng/mL}$, or $\geq 35 \text{ ng/mL}$ with ECG evidence of Q-wave, on days up to and including POD 4; (2) a peak CK-MB $\geq 25 \text{ ng/mL}$ or new Q-wave occurring after POD 4; or (3) a Q-wave or non-Q-wave MI identified by the investigator and confirmed by the CEC. In addition, other previously used criteria¹³ were also applied to the definition of nonfatal MI (and composite end point) as a post hoc analysis. For patients

with CK-MB contributing as at least 1 source of the suspected event, the additional definitions of CK-MB ≥ 70 ng/dL and CK-MB ≥ 100 ng/dL were applied to the adjudicated population to identify patients with more significant myocardial damage.

Patient blood samples were collected before CABG surgery (baseline) and 4, 8, 12, 16, 24, 36, 48, 72, and 96 hours and 30 and 90 days after CABG surgery. All samples were submitted to a central laboratory (Cirion BioPharm Research, Inc, Laval, Quebec, Canada) for CK-MB measurements. Electrocardiograms were performed at baseline, on POD 2, 4, 30, and 90 and analyzed according to the Minnesota Code²¹ by an independent core laboratory (Dynacare Laboratories, Edmonton, Alberta, Canada). All unscheduled CK-MB determinations and ECGs were also recorded and adjudicated by the CEC.

Cerebral infarction was defined as any new sudden onset focal neurologic deficit lasting ≥ 24 hours following exclusion of intracranial hemorrhage by imaging (computed tomography scan or magnetic resonance imaging). All patients suspected clinically of having a stroke or transient ischemic attack were required to undergo a neurologic examination (conducted by a neurologist or internist with expertise in cerebral vascular disease) within 24 hours of onset of symptoms, in addition to cerebral imaging.

Statistical Methods

The sample size estimate assumed a primary event rate of 15% with placebo. In this phase 2 study, a sample size of 300 patients per treatment group had 78% power to detect a relative reduction of 37% in any of the 2 active groups with a 2-sided significance level of .20 for both comparisons with placebo. The primary analysis compared the incidence in each active treatment group with that in the placebo group using 2 χ^2 tests: 1 for the comparison of MC-1 250 mg/d versus placebo and 1 for the comparison of MC-1 750 mg/d versus placebo with no adjustments for multiple comparisons. End points were computed on a per-patient basis. For the components of the primary efficacy end point at POD 30 and for the composite end point at POD 90, χ^2 tests comparing the 3 groups were used. If significant, χ^2 tests with 1 degree of freedom were performed for comparisons against placebo. For the components of the primary efficacy end point at POD 90, analyses were based on time to event and groups were compared using log-rank tests. Again, pairwise comparisons were undertaken only when the overall comparison was significant. Areas under the curve of CK-MB were compared across groups using an analysis of variance. Aside from the primary analysis, all other statistical tests were performed at a significance level of .10.

Trial Organization

A Steering Committee supervised the scientific conduct of the study, and an independent Data and Safety Monitoring Board oversaw safety and ethical issues. The clinical sites, CEC, ECG Core Laboratory, and Central Laboratory shared the responsibility of identifying potential end point events, and the CEC was responsible for adjudicating all of them. Project management, data management, and Canadian site management were conducted by the Montreal Heart Institute Coordinating Center (Montreal, Canada), which also prepared the randomization codes. Site management in the United States was conducted by Duke Clinical Research Institute (Raleigh, NC). Statistical analyses were performed by the

Montreal Heart Institute Coordinating Center independently of the sponsor. Medtronic Inc (Winnipeg, Canada) sponsored the study.

Results

Patient Characteristics

The demographics and clinical characteristics of the 901 randomized patients were relatively well balanced between the 3 treatment groups (Table 1). There were slightly fewer patients with prior MIs, hypertension, heart failure, recent MI, and need for urgent CABG in the placebo group and slightly more patients with prior PCIs, diabetes, and peripheral vascular disease. Overall, the mean patient age was 66 years (range, 34–95 years), and 79% of patients were men. The patients' flow in the study is shown in Figure 1.

Efficacy Analyses

Of the 901 patients, 217 (24.1%) reached the prespecified primary end point at POD 30 defined as cardiovascular death, nonfatal cerebral infarction, and nonfatal MI (peak CK-MB ≥ 50 mg/mL) distributed as follows: 25.1% (75/299) placebo, 21.6% (65/301) 250 mg/d MC-1, and 25.6% (77/301) 750 mg/d MC-1 (Table 2). At 30 days, the 250-mg dose of MC-1 reduced the combined end point of cardiovascular death, nonfatal cerebral infarction, and nonfatal MI by 14.0% ($P = .3124$) with peak CK-MB ≥ 50 ng/mL; 32.3% ($P = .0349$) with peak CK-MB ≥ 70 ng/mL; and 37.2% ($P = .0283$) with peak CK-MB ≥ 100 ng/mL. Compared with placebo, MC-1 250 mg reduced MIs with peak CK-MB ≥ 50 ng/mL by 15.2% ($P = .2988$), MIs with peak CK-MB ≥ 70 ng/mL by 37.6% ($P = .0192$), and MIs with peak CK-MB ≥ 100 ng/mL by 47.2% ($P = .0083$).

MC-1 750 mg did not significantly affect the composite primary end point when more restrictive CK-MB criteria were employed. However, MC-1 750 mg reduced MIs with peak CK-MB ≥ 100 ng/mL by 47.2% ($P = .0083$) compared with placebo at POD 30. Among patients with adjudicated MIs, the area under the curve of CK-MB (0–24 hours) was 1765.5 ± 1148.7 in the placebo group, 1581.5 ± 1071.9 in the MC-1 250-mg group, and 1397.9 ± 962.7 in the MC-1 750-mg arm ($P = .1737$). Finally, similar trends as those described at POD 30 were observed at POD 90 (Table 3).

Safety Analyses

MC-1 administered for 30 days was generally well tolerated. Both in the MC-1 and placebo groups, 69% to 73% of the patients experienced ≥ 1 adverse event from randomization to POD 4 or from POD 4 to end of trial (Table 4). Most events were considered to be mild to moderate in intensity. Notably, the incidence of hypotension up to POD 4 was slightly higher with MC-1 750 mg, as was vomiting from POD 4 to the end of the trial. Finally, the incidence of atrial fibrillation from POD 4 to end of trial was 11.9% with

TABLE 1. Characteristics of the study population

	Placebo (n = 299)	MC-1 250 mg (n = 301)	MC-1 750 mg (n = 301)	All (n = 901)
Sex (% male)	80.3	76.7	79.1	78.7
Age (mean y $\pm$ SD)	66 $\pm$ 10	65 $\pm$ 11	65 $\pm$ 10	66 $\pm$ 10
Race (% Caucasian)	93.3	92.0	93.4	92.9
Previous MI (%)	51.4	58.8	56.3	55.5
Previous PCI (%)	25.8	20.7	20.6	22.4
Previous CABG (%)	3.7	2.7	3.7	3.3
Angina (%)	82.1	79.7	78.1	80.0
Atrial fibrillation (%)	5.1	6.0	4.7	5.2
Silent ischemia (%)	6.8	5.2	8.4	6.8
Hypertension (%)	72.5	77.0	74.4	74.6
Diabetes (%)	46.2	39.6	43.8	43.1
Hypercholesterolemia (%)	82.8	79.7	80.1	80.9
Peripheral vascular disease (%)	17.6	14.4	17.6	16.5
Congestive heart failure (%)	13.5	19.8	15.1	16.1
Current smoker (%)	29.8	27.6	26.8	28.0
History of diabetes mellitus requiring treatment other than diet (%)	43.8	36.5	41.1	40.5
Evidence of LVD or CHF (%)	21.1	30.2	27.8	26.4
History of nondisabling stroke, TIA, or endarterectomy (%)	12.0	12.0	12.9	12.3
Urgent CABG intervention required (%)	71.9	76.4	77.8	75.4
History of MI 48 hours to 6 weeks prior to study entry (%)	24.1	28.6	27.5	26.7
Prior peripheral artery surgery or angioplasty (%)	17.4	12.0	11.3	13.5
Creatinine 133–250 μ mol/L (%)	8.0	8.3	7.9	8.1
Presence of at least 1 carotid artery stenosis >50% (%)	7.7	5.6	5.0	6.1
Age >65 years (% patients)	58.5	54.2	54.6	55.8

MI, Myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafts; TIA, transient ischemic attack; LVD, left ventricular dysfunction; CHF, congestive heart failure.

placebo, 5.7% with MC-1 250 mg, and 6.0% with MC-1 750 mg.

Discussion

The primary result of this study is that MC-1 did not significantly affect the prespecified composite end point of cardiovascular death, nonfatal MI (peak CK-MB level $\geq$ 50 ng/mL), and nonfatal cerebral infarction in this phase 2 study of high-risk CABG patients. However, MC-1 administered at a dose of 250 mg daily in the MEND-CABG trial was associated with a decreased risk for major cardiovascular events with the application of higher thresholds of CK-MB applied to the criteria for MI detection in a post hoc analysis. Reductions of 32.3% and 37.2% of the combined end point of cardiovascular death, nonfatal stroke, and nonfatal MI were obtained with MC-1 when CK-MB cutoff values of 70 and 100 ng/mL were used, respectively, in these exploratory analyses. Furthermore, 250 mg of MC-1 reduced MIs with peak CK-MB $\geq$ 100 ng/mL by 47.2%. Considering that levels of elevated CK-MB in the post-CABG setting correlate with the extent of myocardial infarction as assessed with magnetic resonance imaging,²² post hoc results of the MEND-CABG trial suggest that

MC-1 may be particularly effective in preventing larger, more significant perioperative infarcts.

There is a linear relationship between postoperative CK-MB elevations and 1-year mortality after CABG.^{23,24} In the GUARDIAN trial, peak CK-MB values after CABG of <25, 25 to 49, 50 to 99, and $\geq$ 100 ng/mL were associated with 6-month mortality risks of 3.4%, 5.8%, 7.8%, and 20.2%, respectively.²⁵ In another study of 3812 patients undergoing CABG, the link between peak CK-MB and 3-year mortality was shown only in patients with values above 88 ng/mL.²⁶ Because of this relationship between CK-MB and mortality, several large clinical trials such as PRIMO-CABG have used a cutoff CK-MB value of 100 ng/mL to diagnose perioperative MIs.^{12,13} In the present study, the observed incidence of nonfatal MIs in the placebo group of 23.1% based on criteria utilized for event adjudication (peak CK-MB $\geq$ 50 ng/mL) was much higher than the reported 11% to 14% incidence in similar populations.^{11,13,23} This higher than expected rate of MIs, in contrast with rates of cardiovascular deaths and nonfatal cerebral infarctions that were those we had predicted, suggest that our cutoff CK-MB value used to diagnose MI may have been too low in the peri-CABG setting. When using the

Figure 1. Patient flow in the MEND-CABG study. The 901 randomized patients were all involved in the efficacy analysis using the intent-to-treat approach.

cutoff CK-MB value of 100 ng/mL, the incidence of the composite end point of cardiovascular death, nonfatal cerebral infarction, and nonfatal MI was 16.4% in the placebo group, in line with the rate (15%) we used in our power calculation for this high-risk population.

The reduction in postoperative MIs with 750 mg of MC-1 versus placebo was not larger than that obtained with 250 mg per day. The rate of nonfatal cerebral infarctions

also tended to be higher in the 750-mg arm, an observation that was unexpected and perhaps may have been due to the play of chance. However, it is not clear whether the slightly higher incidence of hypotension associated with 750 mg of MC-1 in the first 4 postoperative days could in part be responsible for this finding. In light of these results, the beneficial effects observed with 250 mg of MC-1 suggest that this dosage may be the preferred one in future trials.

TABLE 2. POD 30 efficacy results—composite and component end points

End point	Placebo (n = 299)	MC-1 250 mg (n = 301)	MC-1 750 mg (n = 301)	P value
Cardiovascular death, nonfatal MI (peak CK-MB ≥ 50 ng/mL), and nonfatal cerebral infarction	75 (25.1%)	65 (21.6%)	77 (25.6%)	.3124 placebo vs 250 mg .8885 placebo vs 750 mg
Cardiovascular death	4 (1.3%)	4 (1.3%)	4 (1.3%)	.9999 (overall)
Nonfatal MI (peak CK-MB ≥ 50 ng/mL)	69 (23.1%)	59 (19.6%)	71 (23.6%)	.4393 (overall)
Nonfatal cerebral infarction	5 (1.7%)	6 (2.0%)	10 (3.3%)	.3642 (overall)
Cardiovascular death, nonfatal MI (peak CK-MB ≥ 70 ng/mL), and nonfatal cerebral infarction	60 (20.1%)	41 (13.6%)	47 (15.6%)	.0349 placebo vs 250 mg .1543 placebo vs 750 mg
Cardiovascular death, nonfatal MI (peak CK-MB ≥ 100 ng/mL), and nonfatal cerebral infarction	49 (16.4%)	31 (10.3%)	34 (11.3%)	.0283 placebo vs 250 mg .0709 placebo vs 750 mg
Nonfatal MI (peak CK-MB ≥ 70 ng/mL)	54 (18.1%)	34 (11.3%)	38 (12.6%)	.0407 (overall) .0192 placebo vs 250 mg .0647 placebo vs 750 mg
Nonfatal MI (peak CK-MB ≥ 100 ng/mL)	43 (14.4%)	23 (7.6%)	23 (7.6%)	.0061 (overall) .0083 placebo vs 250 mg .0083 placebo vs 750 mg

MI, Myocardial infarction; CK-MB, creatinine kinase–myocardial band.

TABLE 3. POD 90 efficacy results—composite and component end points

Endpoint	Placebo (n = 299)	MC-1 250 mg (n = 301)	MC-1 750 mg (n = 301)	P value
Cardiovascular death, nonfatal MI (peak CK-MB $\geq$ 50 ng/mL), and nonfatal cerebral infarction	80 (26.8%)	67 (22.3%)	78 (25.8%)	.4047 (overall)
Cardiovascular death*	4 (1.3%)	5 (1.7%)	4 (1.3%)	.9272 (overall)
Nonfatal MI (peak CK-MB $\geq$ 50 ng/mL)*	74 (24.7%)	60 (19.9%)	72 (23.8%)	.3327 (overall)
Nonfatal cerebral infarction*	5 (1.7%)	6 (2.0%)	11 (3.6%)	.2362 (overall)
Cardiovascular death, nonfatal MI (peak CK-MB $\geq$ 70 ng/mL), and nonfatal cerebral infarction	61 (20.4%)	42 (14.0%)	48 (15.9%)	.0362 placebo vs 250 mg .1516 placebo vs 750 mg
Cardiovascular death, nonfatal MI (peak CK-MB $\geq$ 100 ng/mL), and nonfatal cerebral infarction	50 (16.7%)	32 (10.6%)	35 (11.6%)	.0299 placebo vs 250 mg .0710 placebo vs 750 mg
Nonfatal MI (peak CK-MB $\geq$ 70 ng/mL)	55 (18.4%)	34 (11.3%)	38 (12.6%)	.0289 (overall) .0144 placebo vs 250 mg .0489 placebo vs 750 mg
Nonfatal MI (peak CK-MB $\geq$ 100 ng/mL)	44 (14.7%)	23 (7.6%)	23 (7.6%)	.0037 (overall) .0059 placebo vs 250 mg .0057 placebo vs 750 mg

*Comparison of groups by log-rank test. *MI*, Myocardial infarction; CK-MB, creatinine kinase-myocardial band.

MC-1 was generally well tolerated in this study. The majority of adverse events during the trial were associated with the surgical procedure and not with the study drug. The relatively high incidence of atrial fibrillation, anemia, and pleural effusions was expected in this perioperative setting. The lower incidence of atrial fibrillation observed in the MC-1 groups (5.7% and 6.0%) compared with the placebo group (11.9%) between POD 4 and the end of the trial is

intriguing. Whether this result is due to a direct effect of MC-1 on the atria, reduced atrial stretch secondary to the lower incidence of large myocardial infarcts, or represents simply a chance finding cannot be determined in this trial. Considering the incidence and morbidity associated with atrial fibrillation in the postoperative setting, the effect of MC-1 on atrial fibrillation should be carefully evaluated in future studies.

TABLE 4. Safety results*

Variable	Placebo (n = 294)	MC-1 250 mg (n = 296)	MC-1 750 mg (n = 299)
From randomization to POD 4			
Patients experiencing one or more SAEs	37 (12.6%)	36 (12.2%)	42 (14.0%)
Percent of SAEs considered by the investigator unlikely or not related to MC-1	100%	93.9%	97.3%
Patients experiencing one or more AEs	205 (69.7%)	217 (73.3%)	216 (72.2%)
Percent of AEs considered by the investigator unlikely or not related to MC-1	95.0%	94.9%	94.4%
Atrial fibrillation	54 (18.4%)	56 (18.9%)	63 (21.1%)
Anemia	43 (14.6%)	52 (17.6%)	34 (11.4%)
Hypotension	32 (10.9%)	37 (12.5%)	39 (13.0%)
Nausea	31 (10.5%)	23 (7.8%)	32 (10.7%)
From POD 4 to end of trial			
Patients experiencing one or more SAEs	76 (25.9%)	80 (27.0%)	76 (25.4%)
Percent of SAEs considered by the investigator unlikely or not related to MC-1	94.9%	94.8%	89.4%
Patients experiencing one or more AEs	213 (72.4%)	203 (68.6%)	213 (71.2%)
Percent of AEs considered by the investigator unlikely or not related to MC-1	95.6%	94.0%	93.3%
Pleural effusion	22 (7.5%)	27 (9.1%)	31 (10.4%)
Atrial fibrillation	35 (11.9%)	17 (5.7%)	18 (6.0%)
Nausea	18 (6.1%)	18 (6.1%)	29 (9.7%)
Peripheral edema	20 (6.8%)	23 (7.8%)	22 (7.4%)
Vomiting	10 (3.4%)	8 (2.7%)	20 (6.7%)

*The safety population was comprised of patients who took $\geq$ 1 dose of study medication. *AE*, Adverse event; *SAE*, serious adverse event; *POD*, postoperative day.

P-5'-P, the active ingredient of MC-1, is a metabolite of pyridoxine (vitamin B₆). Although anecdotal evidence suggests a role for vitamin B₆ in cardiovascular health, recent large-scale clinical trials have failed to demonstrate any benefit.^{27,28} In contrast, MC-1 has shown cardioprotective effects in animal models, and data from phase 2 trials are encouraging.²⁰ This discrepancy may be explained by the fact that doses of pyridoxine above 25 mg produce little change in plasma levels of P-5'-P.²⁹ Thus, it is not possible to achieve therapeutic plasma levels of P-5'-P (such as those obtained with the doses of MC-1 used in this study) through vitamin B₆ supplementation. MC-1 is a purinergic P₂-receptor antagonist that inhibits the binding of adenosine triphosphate (ATP) and thereby decreases calcium flux into cardiomyocytes.^{30,31} Extracellular ATP is released from platelets and nerve endings during various stress conditions, such as ischemia or reperfusion injury, and acts on purinergic P₂-receptors on cardiomyocytes to initiate an increase in intracellular calcium. Because calcium overload leads to cell damage and is responsible for cell death during ischemia followed or not by reperfusion, reduction in calcium influx may explain the beneficial effects observed with MC-1 in animal¹⁹ and clinical²⁰ studies. The majority of myocardial infarctions occurred within the first few days after CABG surgery in this study, and the reduction with MC-1 therefore was already observed at POD 4. The phase 2, MEND-CABG trial extends previous results in a much larger study conducted in a population of patients that was at high risk of cardiovascular events, in the setting of myocardial ischemia and reperfusion.

In conclusion, treatment with MC-1 in high-risk patients undergoing CABG with cardiopulmonary bypass did not significantly affect the prespecified primary end point but was associated with a significant reduction in perioperative myocardial infarctions in a post hoc analysis using CK-MB thresholds of 70 and 100 ng/mL. A larger, well-powered trial is needed to further evaluate the cardioprotective effects of MC-1.

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Appendix E1 Participating Centers

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United States—Dr John Harlan and Juli Burks (Medical Center East, Birmingham, Ala); Dr Bleakley Chandler and Paula Easler (University Hospital, Augusta, Ga); Dr Eric Dippel and Penny Stoakes (Genesis Medical Center, Davenport, Iowa); Dr Clay

Burnett and Sandy Bernhardt (Olathe Medical Center, Olathe, Kan); Dr A. David Slater and Elizabeth Cooke (Jewish Hospital, Louisville, Ky); Dr James C. Todd III and Janine Uhrin (Peninsula Regional Medical Center, Salisbury, Md); Dr Norbert Baumgartner and Kathleen Mostek (Covenant Medical Center, Saginaw, Mich); Dr John Fetter and Liz Zappitello (Saint Mary's Medical Center, Duluth, Minn); Dr Timothy Kroshus and Julia Price (Abbott Northwestern Hospital, Minneapolis, Minn); Dr Nicholas Kouchoukos and Nancy Nickerson (Missouri Baptist Medical Center, St Louis, Miss); Dr Joseph Graham and Rita Stiles (St-John's Regional Medical Center, Joplin, Miss); Dr David Duncan and Sherry Duncan (Forsyth Medical Center, Winston-Salem, NC); Dr John Alexander and Ann Skye (Duke University Medical Center, Durham, NC); Dr Paul H. Werner and Cheryl Zywicki (Saint Lukes Medical Center, Milwaukee, Wis); Dr Mohammed Quader and Jacque Taylor (University Nebraska Medical Center, Papillion, Neb); Dr Roberto Novoa and Patricia Boyd (Aultman Hospital, Canton, Ohio); Dr Benjamin Sun and Ana Moore (Ohio State University Medical Center, Columbus, Ohio); Dr Anoar Zacharias and Robert Habib (St-Vincent Mercy Medical Center and Saint Luke's Hospital, Toledo, Ohio); Dr Sanjay Mehta and Paula Ulsh (Milton S. Hershey Medical Center, Hershey, Pa); Dr Paul Risher and Eileen Taff (Saint Luke's Hospital, Bethlehem, Pa); Dr Robert Hagberg and Jennine Zumbuhl (Sentara Norfolk General Hospital, Norfolk, Va); Dr Frederick Armenti and Sandy Watt (McLaren Regional Medical Center, Flint, Mich).