

Original Investigation

Effect of Metformin on Left Ventricular Function After Acute Myocardial Infarction in Patients Without Diabetes

The GIPS-III Randomized Clinical Trial

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IMPORTANCE Metformin treatment is associated with improved outcome after myocardial infarction in patients with diabetes. In animal experimental studies metformin preserves left ventricular function.

OBJECTIVE To evaluate the effect of metformin treatment on preservation of left ventricular function in patients without diabetes presenting with ST-segment elevation myocardial infarction (STEMI).

DESIGN, SETTING, AND PARTICIPANTS Double-blind, placebo-controlled study conducted among 380 patients who underwent primary percutaneous coronary intervention (PCI) for STEMI at the University Medical Center Groningen, the Netherlands, between January 1, 2011, and May 26, 2013.

INTERVENTIONS Metformin hydrochloride (500 mg) (n = 191) or placebo (n = 189) twice daily for 4 months.


MAIN OUTCOMES AND MEASURES The primary efficacy measure was left ventricular ejection fraction (LVEF) after 4 months, assessed by magnetic resonance imaging. A secondary efficacy measure was the N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration after 4 months. The incidence of major adverse cardiac events (MACE; the combined end point of death, reinfarction, or target-lesion revascularization) was recorded until 4 months as a secondary efficacy measure.

RESULTS At 4 months, all patients were alive and none were lost to follow-up. LVEF was 53.1% (95% CI, 51.6%-54.6%) in the metformin group (n = 135), compared with 54.8% (95% CI, 53.5%-56.1%) (P = .10) in the placebo group (n = 136). NT-proBNP concentration was 167 ng/L in the metformin group (interquartile range [IQR], 65-393 ng/L) and 167 ng/L in the placebo group (IQR, 74-383 ng/L) (P = .66). MACE were observed in 6 patients (3.1%) in the metformin group and in 2 patients (1.1%) in the placebo group (P = .16). Creatinine concentration (79 μ mol/L [IQR, 70-87 μ mol/L] vs 79 μ mol/L [IQR, 72-89 μ mol/L], P = .61) and glycated hemoglobin (5.9% [IQR, 5.6%-6.1%] vs 5.9% [IQR, 5.7%-6.1%], P = .15) were not significantly different between both groups. No cases of lactic acidosis were observed.

CONCLUSIONS AND RELEVANCE Among patients without diabetes presenting with STEMI and undergoing primary PCI, the use of metformin compared with placebo did not result in improved LVEF after 4 months. The present findings do not support the use of metformin in this setting.

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Group Information: The Glycometabolic Intervention as Adjunct to Primary Coronary Intervention in ST-Segment Elevation Myocardial Infarction (GIPS-III) Investigators and Committee members are listed at the end of this article.

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In the Western world, approximately 1 of every 7 people with acute myocardial infarction will die of its consequences.^{1,2} Patients presenting with ST-segment elevation myocardial infarction (STEMI) require immediate treatment with antithrombotic agents and primary percutaneous intervention (PCI) to restore coronary blood flow.¹⁻³ Timely reperfusion reduces myocardial damage and the risk of developing left ventricular dysfunction.^{4,5} Still, STEMI results in left ventricular dysfunction in up to 50% of patients, and approximately 20% to 40% of patients develop heart failure sometime after STEMI.^{6,7} Heart failure after STEMI is associated with a 3 to 4 times higher mortality risk.⁷⁻¹⁰ Left ventricular dysfunction is regarded as the strongest predictor for adverse outcome after STEMI.¹

Metformin, a biguanide often used in the treatment of diabetes, has been reported to have favorable effects on ventricular function.¹¹ Basic studies showed that metformin treatment is associated with an enhanced phosphorylation of AMP-activated protein kinase, inducing changes in intracellular pathways and altering mitochondrial function.¹² Interference with these pathways may ultimately result in improved systolic and diastolic function. Data from experimental studies have suggested that administration of metformin before and during ischemia-reperfusion might affect these protective pathways and preserve left ventricular function, independent of glycometabolic state.¹³⁻¹⁵ Moreover, in observational studies of patients with acute myocardial infarction, concurrent treatment with metformin was associated with lower peak values of creatine kinase (CK), myocardial band of CK, and troponins and with improved survival after STEMI in patients with type 2 diabetes, compared with other antihyperglycemic strategies.¹⁶⁻¹⁸

The Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction (GIPS) III trial was designed to determine whether metformin preserves left ventricular function after STEMI in patients without diabetes.¹¹

Methods

Study Population

All patients admitted to the University Medical Center Groningen between January 1, 2011, and May 26, 2013, via the STEMI protocol were considered eligible for this trial. The design of the study has been described in detail previously.¹¹ Briefly, inclusion criteria were age older than 18 years, the presence of STEMI, and primary PCI with implantation of at least 1 stent with a diameter of at least 3 mm resulting in Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 post PCI. Major exclusion criteria were previous myocardial infarction, known diabetes, the need for coronary artery bypass graft surgery, severe renal dysfunction, and standard contraindications for magnetic resonance imaging (MRI).

Study Procedures

On admission, standard laboratory assessment including serum concentrations of CK, myocardial band of CK, creati-

nine, N-terminal pro brain natriuretic peptide (NT-proBNP), blood glucose, and glycated hemoglobin (HbA_{1c}) was performed. Standard physical examination parameters including blood pressure, heart rate, and body mass index were measured. Coronary angiography was performed using standard techniques. The choice and order of coronary intervention (ie, thrombus aspiration, balloon angioplasty, or stenting) was left to the discretion of the operator. During the PCI procedure, all patients provided verbal informed consent in the presence of an independent witness.

After arrival in the coronary care unit, patients were randomly assigned in a 1:1 ratio, using block randomization of 6 patients, to a 4-month treatment with either metformin hydrochloride (500 mg) or a visually matching placebo, both administered twice daily, blinded to patients and investigators. The study medication was started as soon as possible after PCI, with the aim of administering the first dose within 3 hours after PCI. The dose of metformin was chosen arbitrarily, based on our experience in the treatment of patients with type 2 diabetes, for whom this would be a typical starting dose.

Manufacturing and packaging including blinding was performed by Stichting Apotheek Haagse Ziekenhuizen, Den Haag, the Netherlands, according to the Good Manufacturing Practice standards of the European Union. Study drug adherence was assessed by tablet counts at the visits to the outpatient clinic. The duration of the treatment, 4 months, was based on the presumption that the majority of myocardial remodeling occurs over the course of this critical period.¹⁹

Following admission to the coronary care unit, patients provided written informed consent. All patients received standard medication according to current guidelines, were offered rehabilitation programs for myocardial infarction, and were given general advice on diet, smoking, and lifestyle changes according to a standardized protocol.¹ Patients were seen in the outpatient clinic 2 weeks, 7 weeks, and 4 months after discharge. Standard laboratory assessment was repeated at 4 months.

Study monitoring, data management, and validation were independently performed at the Trial Coordination Center (University Medical Center Groningen, the Netherlands). Detailed information is available in eMethods 1 in Supplement. The members of the steering committee were responsible for the design and conduct of the trial and the collection of the data. An end point adjudication committee blinded to allocation assessed all end points, and a data and safety monitoring board advised on whether the trial should be stopped because of clear evidence of harm. Members of the publication committee wrote all drafts of the manuscript and vouch for the accuracy and completeness of the reported data.

The contents of this article are consistent with the research protocol, and the data analysis was performed according to a prespecified analysis plan. The study protocol was in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Groningen, the Netherlands) and national regulatory authorities.

Study Outcomes

The primary efficacy measure was left ventricular ejection fraction (LVEF), measured by MRI 4 months after infarction. Imaging was performed on a 3.0 Tesla whole-body MRI scanner (Achieva; Philips) using a phased array cardiac receiver coil. Electrocardiogram-gated cine steady state, free precession magnetic resonance images were acquired during repeated breath holds in contiguous short-axis slices of 1 cm covering the entire left ventricle. The endocardial borders were outlined in end-systolic and end-diastolic images. Left ventricular end-systolic volumes and left ventricular end-diastolic volumes were calculated using the summation of slice method multiplied by slice thickness. An independent core laboratory (Image Analysis Center, VU University Medical Center, Amsterdam, the Netherlands) evaluated the MRI scans and assessed the primary efficacy measure, blinded for treatment allocation and clinical patient data.

One of the principal secondary efficacy measures was the NT-proBNP concentration at 4 months. Before unblinding the study we prioritized the NT-proBNP levels at 4 months as the principal secondary efficacy measure, above other collected outcome measures, based on the strong evidence for NT-proBNP level as an independent predictor of clinical outcome.²⁰ Other secondary efficacy measures were the incidence, within 4 months after infarction, of the combined end point major adverse cardiac events (MACE [cardiovascular death, recurrent myocardial infarction, target-lesion revascularization]), and single efficacy and safety measures consisting of death, recurrent STEMI and non-ST-segment elevation myocardial infarction, recurrent coronary intervention (excluding interventions solely based on baseline, pretreatment angiography and clinical information), target-lesion revascularization, target-vessel revascularization, non-target-vessel revascularization, coronary artery bypass graft surgery, hospitalization for heart failure, hospitalization for chest pain, implantation of an implantable cardioverter-defibrillator, stroke, and lactic acidosis. The definitions used are available in eMethods 2 in Supplement.

Concentrations of glucose and HbA_{1c} were recorded at 4 months as additional efficacy measures, whereas creatinine concentration was recorded as an additional safety parameter.

Statistical Analysis

The study was designed with 80% power to detect a significant difference in LVEF between the 2 groups 4 months after STEMI, at a 2-sided significance level of 5%. Previous randomized trials in patients with acute myocardial infarction that showed reduced mortality and morbidity demonstrated concurrent absolute differences in LVEF of 3 percentage points or more.^{21,22} Therefore, we considered this to be a feasible and clinically important difference. The SD of the effect measure was estimated to be 9%.²³ We calculated that 141 patients would need to be enrolled in each group. To allow an estimated 12% of patients to not undergo the primary end point measurement, we increased the initial total sample size to 320 patients. Actual dropout rates were close to 25%, resulting in the recommendation by the data and safety monitoring board to

increase the total sample twice, first to 350 patients and then to 380 patients. To maintain statistical power to detect a clinically significant difference, these recommendations were acknowledged by the steering committee.

All analyses were performed according to a prespecified statistical analysis plan, which was finalized prior to unblinding of the randomization code (available from authors). Values for continuous variables that approximate a normal distribution are presented as mean (SD), and differences between groups were assessed by 2-tailed *t* test. Continuous variables not normally distributed are presented as medians with their interquartile ranges (IQRs). If normality could not be assumed, data underwent log transformation to convert it to a normal distribution. If indicated, differences in effect measurements and their 95% confidence intervals are presented between the control group and the metformin group. A sensitivity analysis using standard linear regression analysis was performed adjusted for age, sex, baseline NT-proBNP concentration, and myocardial blush grade to evaluate the robustness of the effect of treatment on the outcome parameters.

Post hoc, we explored multiple-imputation analysis ($M = 100$) as implemented in Stata under the *mi* command. We used ordered logistic (*olog*) regression to impute the 3 missing myocardial blush grade values. We used multivariate normal regression (*mvn*) for missing continuous variables (108 missing LVEF and 5 missing HbA_{1c} values), which uses a Bayesian iterative Markov Chain Monte Carlo method to impute missing values. We explored 2 strategies of imputing missing values: strategy A, based on age, sex, myocardial blush grade, and baseline NT-proBNP values (the variables used for the multivariate sensitivity analysis) and strategy B, based on all available Table 1 baseline variables (glucose and claudication were omitted because of collinearity). χ^2 Analysis or Fisher exact test was used to test differences between proportions of presence of a clinical secondary efficacy measure as adjudicated by the end point adjudication committee.

All reported *P* values are 2-sided, and $P < .05$ was considered to indicate a significant difference between groups. Analyses were performed with Stata version 12.0 (StataCorp).

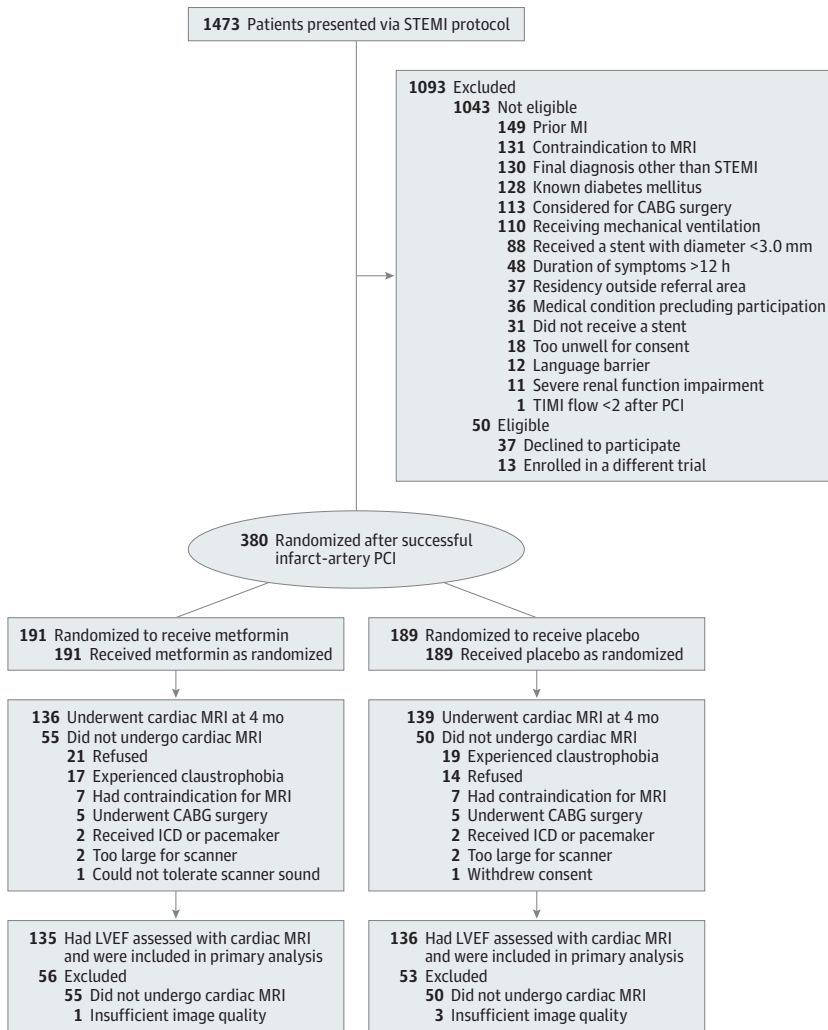
Results

Study Population

During the enrollment period, between January 1, 2011, and May 26, 2013, 1473 patients were admitted to our hospital via the STEMI protocol (Figure 1). After inclusion and exclusion criteria were considered and verbal informed consent obtained, a total of 380 patients were enrolled in the study. Of the total sample, 191 patients were randomly allocated to the metformin treatment and 189 patients to placebo. Following admission to the coronary care unit, all patients provided written informed consent, except for 1 (randomized to placebo). This patient withdrew verbal consent and was excluded from analysis, leaving 379 patients in the final study.

Baseline characteristics at randomization were well balanced in the 2 treatment groups (Table 1). The median time from the onset of symptoms to first coronary intervention was

Figure 1. Flow of Patients Through the Glycometabolic Intervention as Adjunct to Primary Coronary Intervention in the ST-Segment Elevation Myocardial Infarction (GIPS-III) Trial



Patients could be excluded for more than 1 reason; the primary reason for exclusion in each case is shown. CABG indicates coronary artery bypass graft; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention.

161 minutes (IQR, 109-250). The median time of administration of the first dose of study treatment after first coronary intervention was 102 minutes in the metformin group (IQR, 81-133) and 100 minutes in the control group (IQR, 78-134) ($P = .27$). The median duration of exposure to study medication was 124 days in the metformin group (IQR, 119-125) and 124 days in the control group (IQR, 120-125) ($P = .14$). The rate of premature discontinuation of the study drug was similar between the metformin and placebo groups (16% vs 13%; $P = .42$). Further details on the medical therapy at discharge are reported in eTable 1 in Supplement.

Cardiac MRI Population

Four months after infarction, all patients were alive and none were lost to follow-up. Of these, 105 patients did not undergo MRI for various reasons (Figure 1). From among the 275 remaining patients, the MRI core laboratory considered 4 scans to be of insufficient quality. On average, patients with MRI data were on average younger, more often male, less often current

smokers, had lower systolic blood pressure, less often had multivessel disease, and more often had better angiographic PCI outcome, as reflected by TIMI flow grade 3 after PCI (eTable 2 in Supplement). There were no baseline differences between the 2 treatment groups (eTable 3 in Supplement).

Primary End Point Measure

Left ventricular ejection fraction 4 months after randomization did not differ between the metformin group (53.1% [95% CI, 51.6%-54.6%]) and the placebo group (54.8% [95% CI, 53.5%-56.1%]) $P = .10$ (Table 2). Additional sensitivity analysis, adjusting for age, sex, baseline NT-proBNP level, and myocardial blush grade suggested that this finding was robust and not driven by potential relevant baseline characteristics. Results were little changed when missing data were handled using multiple imputations. The treatment effect on LVEF was also similar in the prespecified subgroups, with the exception being the subgroup divided according to the median creatinine level (Figure 2). However, when creatinine levels were studied on

a continuous scale, no evidence for interaction with the effect of metformin was observed (interaction coefficient, 0.03 [95% CI, -0.11 to 0.17]; $P = .69$), suggesting that this finding is attributable to chance.

Secondary End Point Measures

The NT-proBNP concentration at 4 months after infarction, a principal secondary efficacy measure, was available in 320 patients (84.4%). The concentration of NT-proBNP was not dif-

Table 1. Baseline Characteristics

| Characteristic | No. (%) | | |
|----------------------------------------------|-----------------|---------------------|-------------------|
| | Total (n = 379) | Metformin (n = 191) | Placebo (n = 188) |
| Age, mean (SD), y | 58.8 (11.6) | 58.7 (11.8) | 58.8 (11.5) |
| Women | 95 (25.1) | 47 (24.6) | 48 (25.5) |
| Body mass index, mean (SD) ^a | 27.0 (3.8) | 26.9 (3.8) | 27.0 (3.9) |
| Race/ethnicity | | | |
| White | 365 (96.3) | 185 (96.9) | 180 (95.7) |
| Asian | 10 (2.6) | 5 (2.6) | 5 (2.7) |
| Black | 4 (1.1) | 1 (0.5) | 3 (1.6) |
| Cardiovascular related history | | | |
| Hypertension | 112 (30.0) | 61 (31.9) | 51 (27.1) |
| Dyslipidemia | 239 (63.1) | 111 (58.1) | 128 (68.1) |
| Current smoking | 209 (55.1) | 108 (56.5) | 101 (53.7) |
| Stroke | 3 (0.8) | 2 (1.0) | 1 (0.5) |
| Peripheral artery disease | 0 | 0 | 0 |
| Previous PCI | 3 (0.8) | 1 (0.5) | 3 (1.6) |
| Blood pressure, mean (SD), mm Hg | | | |
| Systolic | 134 (23) | 135 (23) | 134 (24) |
| Diastolic | 84 (15) | 85 (14) | 84 (15) |
| Heart rate, mean (SD), beats/min | 76 (16) | 75 (16) | 77 (16) |
| Ischemia time, median (IQR), min | 161 (109-250) | 171 (110-272) | 153 (108-234) |
| Single-vessel disease | 258 (68.1) | 122 (63.0) | 136 (72.3) |
| Infarct-related artery | | | |
| Left main | 0 | 0 | 0 |
| Left anterior descending coronary artery | 146 (38.5) | 75 (39.3) | 71 (37.8) |
| Left circumflex coronary artery | 64 (16.9) | 33 (17.3) | 31 (16.5) |
| Right coronary artery | 169 (44.6) | 83 (43.5) | 86 (45.7) |
| Infarct-related artery TIMI flow | | | |
| Preintervention grade | | | |
| 0 | 208 (54.9) | 99 (51.8) | 109 (58.0) |
| 1 | 27 (7.1) | 14 (7.3) | 13 (6.9) |
| 2 | 66 (17.4) | 45 (23.6) | 21 (11.2) |
| 3 | 78 (20.6) | 33 (17.3) | 45 (23.9) |
| Postintervention grade | | | |
| 2 | 34 (9.0) | 24 (12.6) | 10 (5.3) |
| 3 | 345 (91.0) | 167 (87.4) | 178 (94.7) |
| Myocardial blush grade | | | |
| 0 | 10 (2.6) | 6 (3.2) | 4 (2.1) |
| 1 | 29 (7.7) | 20 (10.6) | 9 (4.8) |
| 2 | 74 (19.5) | 35 (18.6) | 39 (20.7) |
| 3 | 263 (69.4) | 127 (67.6) | 136 (72.3) |
| Laboratory values at admission, median (IQR) | | | |
| CK, U/L | 129 (83-210) | 133 (87-260) | 123 (82-181) |
| Myocardial band of CK, U/L | 16 (13-25) | 16 (13-29) | 16 (12-23) |
| Creatinine, μ mol/L | 72 (62-82) | 71 (61-84) | 72 (63-80) |
| NT-proBNP, ng/L | 81 (40-200) | 83 (41-235) | 79 (38-176) |
| Glucose, mmol/L | 8.2 (7.0-9.6) | 8.2 (7.0-9.4) | 8.4 (7.2-9.8) |
| HbA _{1c} , % | 5.8 (5.6-6.0) | 5.8 (5.6-6.1) | 5.8 (5.6-6.0) |

Abbreviations: CK, creatine kinase; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; NT-proBNP, N-terminal pro brain natriuretic peptide; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

^a Calculated as weight in kilograms divided by height in meters squared.

Table 2. Outcomes at 4 Months

| Outcome ^a | Total (n = 379) | Metformin (n = 191) | Placebo (n = 188) | P Value |
|-----------------------------------------------------|--------------------|------------------------|----------------------|---------|
| Primary end point, % (95% CI) | | | | |
| LVEF | 53.9 (52.9-55.0) | 53.1 (51.6-54.6) | 54.8 (53.5-56.1) | .10 |
| Secondary end point, median (IQR) | | | | |
| NT-proBNP, ng/L | 167 (72-390) | 167 (65-393) | 167 (74-375) | .66 |
| Creatinine, μ mol/L | 79 (71-88) | 79 (70-87) | 79 (72-89) | .61 |
| Glucose, mmol/L | 5.7 (5.2-6.2) | 5.7 (5.2-6.3) | 5.6 (5.2-6.2) | .96 |
| HbA _{1c} , % | 5.9 (5.7-6.1) | 5.9 (5.6-6.1) | 5.9 (5.7-6.1) | .15 |
| Clinical outcomes, No. (%) | | | | |
| MACE ^b | 8 (2.1) | 6 (3.1) | 2 (1.1) | .16 |
| Death | 0 | 0 | 0 | 1.00 |
| Reinfarction | 7 (1.8) | 5 (2.6) | 2 (1.1) | .26 |
| STEMI | 2 (0.5) | 1 (0.5) | 1 (0.5) | .99 |
| Non-STEMI | 5 (1.3) | 4 (2.1) | 1 (0.5) | .18 |
| Stent thrombosis | 3 (0.8) | 2 (1.0) | 1 (0.5) | .57 |
| Ischemia-driven reintervention | 15 (4.0) | 8 (4.2) | 7 (3.7) | .82 |
| Target-lesion revascularization | 4 (1.1) | 3 (1.6) | 1 (0.5) | .33 |
| Target-vessel revascularization | 3 (0.8) | 1 (0.5) | 2 (1.1) | .56 |
| Non-target-vessel revascularization | 8 (2.1) | 4 (2.1) | 4 (2.2) | .99 |
| CABG surgery | 1 (0.3) | 1 (0.5) | 0 | .32 |
| Hospitalization for heart failure | 2 (0.5) | 2 (1.0) | 0 | .16 |
| Hospitalization for chest pain | 24 (6.3) | 14 (7.3) | 10 (5.3) | .42 |
| Implantable cardioverter-defibrillator implantation | 3 (0.8) | 2 (1.0) | 1 (0.5) | .57 |
| Stroke | 1 (0.3) | 0 | 1 (0.5) | .31 |
| Diabetes | 59 (15.6) | 32 (18.5) | 27 (15.3) | .56 |

Abbreviations: CABG, coronary artery bypass graft; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; non-STEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; STEMI, ST-segment elevation myocardial infarction.

^a Definitions are available in eMethods 2 in Supplement.

^b Death, reinfarction, or target-lesion revascularization.

ferent between the 2 groups, with a median of 167 ng/L (IQR, 65-393 ng/L) for the metformin group and 167 ng/L (IQR, 74-375 ng/L) for the placebo group ($P = .66$). This finding did not change in sensitivity analysis with adjustment for age, sex, baseline NT-proBNP concentration, and myocardial blush grade.

The combined MACE end point and individual end points—reinfarction, interventions, hospitalizations for heart failure and chest pain, implantations of implantable cardioverter-defibrillators, and stroke—up to 4 months are displayed in Table 2. No differences in MACE were observed between the metformin group compared with the placebo group (3% vs 1%, respectively; $P = .16$). There were also no differences in individual end points between the 2 treatment groups. There were no significant differences between the patients who underwent primary end point assessment and those who did not undergo MRI (eTable 4 in Supplement). The study medication was generally well tolerated. No case of lactic acidosis and impaired renal function was diagnosed during follow-up.

Concentrations of creatinine, glucose, and HbA_{1c} were available in 333 (87.8%), 328 (86.5%), and 317 (83.6%) patients, respectively. The creatinine concentration at 4 months was comparable between the metformin group (79 μ mol/L [IQR, 70-87 μ mol/L]) and the control group (79 μ mol/L [IQR, 72-89 μ mol/L]) ($P = .61$). Glucose levels measured at 4 months during the visit to the outpatient clinic were 5.7 mmol/L (IQR, 5.2-6.3 mmol/L) in the metformin group and 5.6 mmol/L (IQR, 5.2-6.2 mmol/L) in the placebo group ($P = .96$). The HbA_{1c} con-

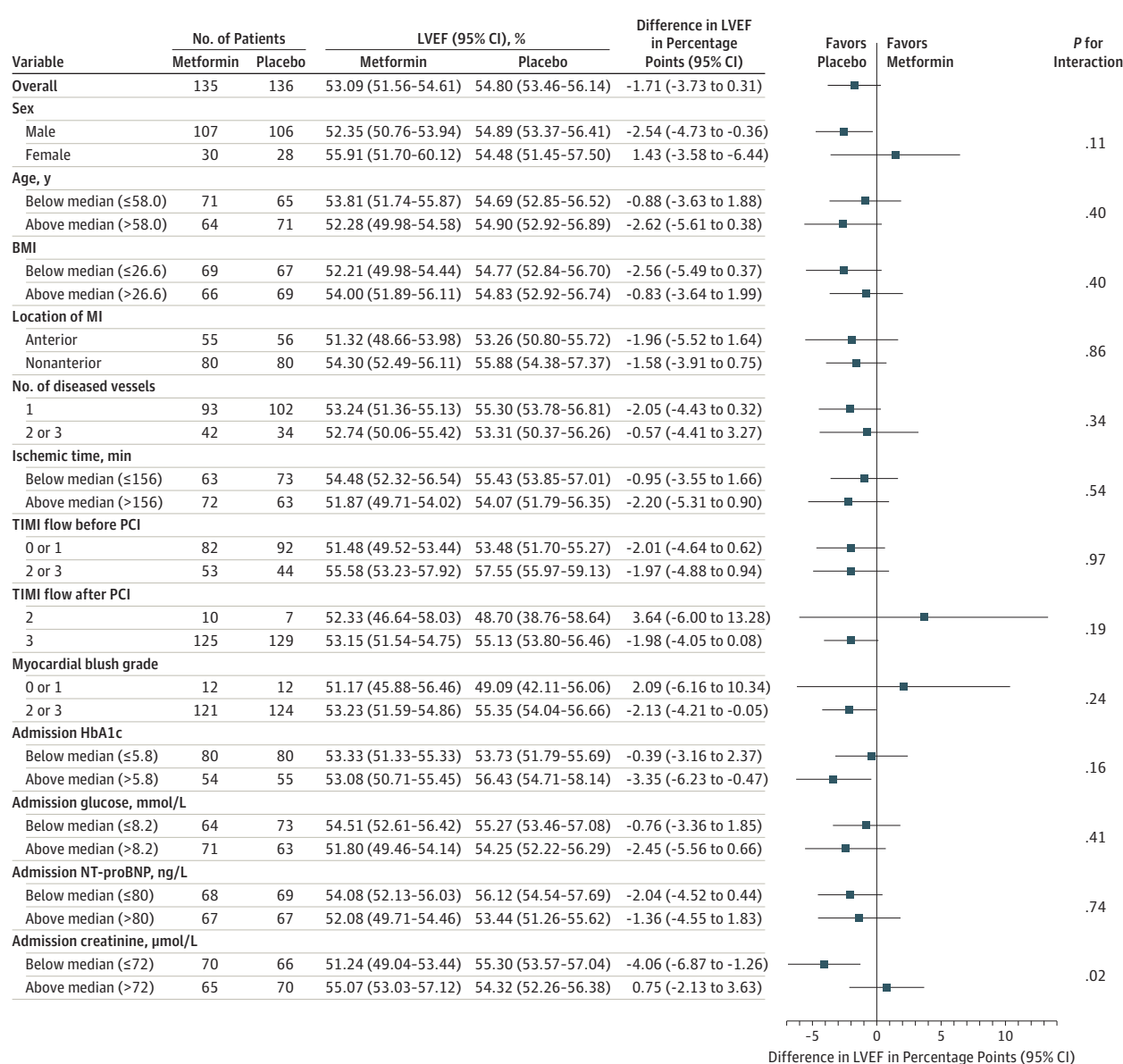
centration at 4 months did not differ between groups, with a median of 5.9% (IQR, 5.6%-6.1%) for the metformin group and 5.9% (IQR, 5.7%-6.1%) for the placebo group ($P = .15$).

Discussion

In this double-blind, randomized, controlled trial, in patients without diabetes who underwent primary PCI for STEMI, treatment with 500 mg of metformin administered twice daily for 4 months did not have an effect on LVEF or NT-proBNP levels, compared with placebo. Because left ventricular function is currently regarded as the most important predictor of morbidity and mortality after STEMI, it is unlikely that metformin will have a significant effect on long-term outcome after STEMI in patients without diabetes.

To our knowledge, this study is the first to prospectively study the effects on left ventricular function of metformin compared with placebo as adjunct to optimal medical treatment. Our results did not confirm the effects observed in experimental studies.¹³⁻¹⁵ In a nondiabetic rat model of myocardial infarction our group demonstrated that metformin was associated with a reduced infarct size of 22% and a relative improvement in LVEF of 52% as compared with placebo.¹³ Another experimental study by Calvert et al¹⁵ demonstrated that administration of metformin both prior to or during ischemia-reperfusion was effective in improving left ventricular function in a mouse model.

Figure 2. Estimated Effect of Metformin Compared With Placebo on Left Ventricular Ejection Fraction (LVEF) According to Prespecified Subgroups



Estimation of the effect of metformin compared with placebo on LVEF according to prespecified subgroups. The estimated LVEF for the effect of metformin in the prespecified subgroups, as well as the absolute difference in LVEF for the effect of metformin per prespecified subgroup compared with the

LVEF in the placebo group is displayed. BMI indicates body mass index; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Therefore, in our attempt to translate these experimental data into clinical situations, we included patients and started metformin immediately after PCI. Furthermore, because experimental data suggest that the effect of metformin on left ventricular function is not solely driven by glycemic control, we studied patients without known diabetes at inclusion.¹³⁻¹⁵ In addition, in patients with established type 2 diabetes, metformin is indicated as standard treatment according to current guidelines; therefore, randomization of these patients to placebo is not appropriate.²⁴

Earlier preclinical studies reporting on the protective effects of metformin were mainly performed in animals undergoing occlusion of the left main or the proximal left anterior descending coronary artery, resulting in a large area at risk.¹³⁻¹⁵ To decrease heterogeneity of baseline LVEF, we only included patients presenting with their first acute myocardial infarction. Because of the exclusion of patients with prior myocardial infarction, as well as those with diabetes or those unable to provide informed consent, the baseline characteristics of our study population are somewhat favorable and lower-risk com-

pared with real-life practice. The exclusion of these high-risk categories might have influenced our findings.^{8,9} However, in our subgroup analyses and in our sensitivity analyses adjusting for TIMI flow and myocardial blush grade, we did not find any evidence that the effect of metformin treatment was dependent on the area at risk.

Another potential reason for the lack of efficacy of metformin in our study might have been the time window between coronary occlusion and achieving effective plasma levels of metformin. On average, the administration of the first dose of study medication took place 101 minutes after coronary intervention. Considering a time to peak plasma concentration of metformin after oral administration of approximately 180 minutes, the average time between PCI and the achievement of effective plasma levels was approximately 4 hours.²⁵ Therefore, our study does not exclude a potential beneficial effect of effective plasma metformin levels during reperfusion or earlier.²⁶

In a retrospective analysis, long-term metformin treatment in patients with diabetes was associated with lower peak levels of biochemical markers of myocardial infarct size and improved outcome compared with other glucose-lowering therapies.^{18,27-29} However, data derived from nonrandomized, retrospective studies are susceptible to prescribing biases. Recently, metformin treatment (250 mg 3 times daily) in patients with the metabolic syndrome started 7 days prior to elective PCI resulted in both a smaller cardiac biomarker release after intervention and a favorable 1-year clinical outcome.³⁰ In experimental animal studies, the beneficial effects of metformin on left ventricular function and myocardial infarct size were similar when metformin was administered prior to or during ischemia-reperfusion.¹⁵ In additional subgroup analyses, we did not observe differences in the treatment effect of metformin dependent on the timing of the first dose.

In addition, the lack of efficacy of metformin in our study might have been attributable to the dose of metformin administered. We studied metformin at a dosage of 500 mg twice daily because this is generally well tolerated and allows open-label treatment of metformin when diabetes is diagnosed after randomization. Another reason not to choose the highest possible dose are reports on metformin-induced lactic acidosis,

especially in acute conditions related to renal insufficiency.^{31,32} Patients with STEMI undergoing acute catheterization with contrast are indeed prone to the development of nephropathy, and safety data on high-dose metformin treatment were not available.³³ In this study, there was no evidence of lactic acidosis or impaired renal function. However, we cannot exclude a potential beneficial effect on LVEF of high-dose metformin treatment.

Four months of treatment with metformin (500 mg twice daily) did not have a large effect on glycemic control. Median glucose and HbA_{1c} levels did not differ between patients receiving metformin compared with placebo ($P = .96$ and $P = .15$, respectively). In the CAMERA (Carotid Atherosclerosis: Metformin for Insulin Resistance) study, treatment of patients with coronary artery disease but without diabetes using metformin (850 mg twice daily for 18 months) resulted in a small but significant difference of -0.13% in HbA_{1c} values.³⁴ Recently, a systemic review of antihyperglycemic therapies to prevent the onset of diabetes could not detect a significant effect of metformin.³⁵ In line with these previous observations, we did not see a difference in the incidence of new-onset diabetes at 4 months.

In our study, measures of left ventricular function were the main end points to investigate the effect of metformin. Left ventricular ejection fraction obtained by MRI is an established efficacy measure because it predicts MACE.³⁶ Concentration of NT-proBNP as a measure strongly relates with LVEF and clinical outcome.^{20,37,38} By using these surrogate measures for clinical outcome we aimed to detect an effect of metformin on outcome. Moreover, we anticipated that the number of MACE would be too small to detect a significant effect of metformin. Indeed, MACE were observed in few patients. Follow-up is ongoing to investigate long-term effects of metformin on clinical outcome.

Conclusions

Among patients without diabetes presenting with STEMI, metformin did not preserve LVEF compared with placebo. A role for metformin in preventing heart failure after myocardial infarction remains unproven.

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