

The effect of metformin on cardiovascular risk profile in patients without diabetes presenting with acute myocardial infarction: data from the Glycometabolic Intervention as adjunct to Primary Coronary Intervention in ST Elevation Myocardial Infarction (GIPS-III) trial

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ABSTRACT

Objective: In patients with diabetes mellitus, metformin treatment is associated with reduced mortality and attenuation of cardiovascular risk. As a subanalysis of the Glycometabolic Intervention as adjunct to Primary Coronary Intervention in ST Elevation Myocardial Infarction (GIPS-III) study, we evaluated whether metformin treatment in patients with ST-segment elevation myocardial infarction (STEMI) without diabetes improves the cardiovascular risk profile.

Methods: A total of 379 patients, without known diabetes, presenting with STEMI were randomly allocated to receive metformin 500 mg twice daily or placebo for 4 months.

Results: After 4 months, the cardiovascular risk profile of patients receiving metformin (n=172) was improved compared with placebo (n=174); glycated hemoglobin (5.83% (95% CI 5.79% to 5.87%) vs 5.89% (95% CI 5.85% to 5.92%); 40.2 mmol/mol (95% CI 39.8 to 40.6) vs 40.9 mmol/mol (40.4 to 41.2), p=0.049); total cholesterol (3.85 mmol/L (95% CI 3.73 to 3.97) vs 4.02 mmol/L (95% CI 3.90 to 4.14), p=0.045); low-density lipoprotein cholesterol (2.10 mmol/L (95% CI 1.99 to 2.20) vs 2.3 mmol/L (95% CI 2.20 to 2.40), p=0.007); body weight (83.8 kg (95% CI 83.0 to 84.7) vs 85.2 kg (95% CI 84.4 to 86.1), p=0.024); body mass index (26.8 kg/m² (95% CI 26.5 to 27.0) vs 27.2 kg/m² (95% CI 27.0 to 27.5), p=0.014). Levels of fasting glucose, postchallenge glucose, insulin, high-density lipoprotein cholesterol, and blood pressure were similar in both groups.

Conclusions: Among patients with STEMI without diabetes, treatment with metformin for 4 months resulted in a modest improvement of the cardiovascular risk profile compared with placebo.

Trial register number: NCT01217307.

Key messages

- In patients with acute myocardial infarction at risk for diabetes, 4 months of treatment with metformin on top of optimal treatment resulted in a modestly more favorable cardiovascular risk profile compared with placebo.
- Perhaps the most important and clinically the most relevant observation was the reduction in weight gain associated with metformin use. Weight loss may be the key factor responsible for metformin's alleged cardioprotective effects.
- Metformin resulted in an improvement of cholesterol levels on top of optimal statin therapy.

INTRODUCTION

After ST-segment elevation myocardial infarction (STEMI), secondary prevention therapies as recommended by current guidelines such as β -blockers, ACE inhibitors, platelet aggregation inhibitors (acetylsalicylic acid and others), and lipid-lowering drugs all have been proven to reduce mortality and attenuate cardiovascular risk profile.¹ In addition to the targeted substrates by current therapies, such as blood pressure, neuroendocrine activation, and increased thrombogenicity, glycometabolic dysregulation is strongly associated with adverse outcome after STEMI.² Impaired fasting glucose and insulin resistance is associated with impaired prognosis, even at levels of dysglycemia not yet diagnostic of diabetes mellitus.^{3–5} Dysglycemia is common in patients with STEMI—as much as one in every four patients have undiagnosed diabetes and up

to one in every two patients has prediabetes.⁶ Although glycometabolic dysregulation is both common and strongly associated with adverse outcomes after STEMI, it nonetheless is not a target of current pharmacotherapy.

Metformin is an effective glucose-lowering biguanide and currently the most widely used oral antihyperglycemic agent.⁷ Metformin has been shown to improve cardiovascular outcome, with a benefit that exceeds the benefit that may be expected solely by blood glucose lowering.^{8–18} In patients with diabetes mellitus and cardiovascular disease, metformin was associated with reduced all-cause mortality compared with other antihyperglycemic strategies.^{8–11} Long-term metformin treatment in patients at risk for or with diabetes improved cardiovascular risk profile mediated by weight loss, improved insulin resistance, reduction of the metabolic syndrome, and by lowering total and low-density lipoprotein (LDL) cholesterol.^{13–21} Further, in patients at risk for diabetes, but without cardiovascular disease, metformin reduced diabetes development with 30–40%.^{13–16}

We aimed to evaluate if metformin treatment, on top of standard care, would improve cardiovascular risk in patients without diabetes. We therefore conducted this prespecified subanalysis in the ‘Metabolic Modulation With Metformin to Reduce Heart Failure After Acute Myocardial Infarction: Glycometabolic Intervention as adjunct to Primary Coronary Intervention in ST Elevation Myocardial Infarction (GIPS-III)’ study, that enrolled patients without diabetes who underwent primary percutaneous coronary intervention (PCI) for STEMI.

METHODS

The study design and baseline characteristics of the single-center, randomized, double-blind, placebo-controlled GIPS-III trial have been reported previously.^{22–23} In brief, patients presenting at the University Medical Center Groningen between January 1, 2011 and May 26, 2013 who underwent acute catheterization for suspicion of STEMI were considered for this trial. Patients older than 18 years who underwent a successful primary PCI with implantation of at least one stent were eligible. Exclusion criteria were known diabetes (defined as documented history of diabetes, current use of antihyperglycemic medication or verbal confirmation by the patient, or glycated hemoglobin (HbA1c) of $\geq 6.5\%$ (48 mmol/mol) prior to admission),²⁴ previous myocardial infarction, severe renal dysfunction, need for coronary artery bypass grafting, conditions resulting in inability to provide informed consent, and conditions that interfered with the ability to comply with the protocol.

The study protocol was in accordance with the Declaration of Helsinki (Fortaleza, 2013), Dutch laws, and was approved by the local ethics committee (Groningen, the Netherlands) and national regulatory

authorities. The study received financial support from the Netherlands Organization for Medical Research (ZonMw; grant nr. 95103007); the funding source had no role in the study.

Procedures

The study procedures and main outcomes have been described in detail.^{22–23} In short, immediately after coronary angiography and subsequent coronary intervention, 379 patients were randomly allocated to metformin 500 mg or visually matching placebo, both administered twice daily. Patients provided verbal informed consent during the PCI procedure and the first dose was administered immediately after arrival at the coronary care unit (CCU).

At admission, body weight, height, blood pressure, and heart rate were measured, and body mass index (BMI) was calculated. Blood was drawn during primary PCI, and blood glucose, HbA1c, insulin, creatinine, and cholesterol levels were assessed. A detailed history including cardiovascular risk profile was assessed during hospitalization. Patients arriving at the CCU between 00:00 and 20:59 were subjected to a standardized oral glucose tolerance test (OGTT) with 75 g of glucose (dissolved in 200 mL water) the following morning.²⁴ In patients arriving at the CCU between 21:00 and 23:59, the OGTT was performed the second morning after admission. During the OGTT in the CCU all patients had already taken at least one to maximally four tablets of study medication. All patients received standard medication according to current guidelines, received counseling on diet, smoking, and lifestyle and were offered a cardiac rehabilitation programme.^{1–25} Patients who were diagnosed with new-onset diabetes were seen by an endocrinologist.

Patients visited the outpatient clinic 2 weeks, 7 weeks, and 4 months after discharge. At 4 months, a standardized OGTT was performed after an overnight fast of at least 8 h. In order to assess whether the study medication actually affected underlying dysglycemia rather than masking its presence, the OGTT was scheduled at least 3 days after stopping the study medication.

End points and definitions

Primary outcomes in this prespecified analysis from the GIPS-III trial were levels of, and change in HbA1c, fasting glucose, postchallenge glucose, insulin levels, cholesterol levels, body weight, BMI, and blood pressure at 4 months, adjusting for baseline levels.

Analysis of glucose, hemoglobin, creatinine, and total cholesterol, LDL-cholesterol, high-density lipoprotein (HDL) cholesterol was performed as part of standard care on standard laboratory assays (Roche Modular, Roche Mannheim, Germany). HbA1c was measured using an immunochemical assay (Tosoh G8, Tosoh Bioscience Inc, South San Francisco, USA). Insulin levels were determined post hoc from blood samples stored at -80°C on a chemoluminescence immunoassay

(Architect i2000 SR Immunoassay analyzer, Abbott Diagnostics, Abbott Park Illinois, USA). Blood samples, other than specific glucose samples for assessment of fasting glucose, were non-fasting samples.

An independent end point adjudication committee, blinded to treatment allocation, using data on HbA1c levels, OGTT, and use of medication assessed diabetic state. Diabetes was defined as an HbA1c of $\geq 6.5\%$ (48 mmol/mol), and/or a fasting blood glucose of ≥ 7.0 mmol/L and/or a 2 h postchallenge blood glucose concentration of ≥ 11.1 mmol/L; prediabetes as an HbA1c between 5.7% (39 mmol/mol) and 6.4% (47 mmol/mol), and/or a fasting blood glucose of 5.6–6.9 mmol/L, and/or a 120 min postchallenge blood glucose 7.8–11.0 mmol/L; patients not meeting any of these criteria were classified as normoglycemic.²⁴

Statistical analyses

Continuous variables are reported as means \pm SD or medians (IQR) for normally and non-normally distributed data, respectively. Differences between groups were tested using Student t test or analysis of variance for normally distributed data, and Wilcoxon or Kruskal-Wallis tests for non-normally distributed data. Differences in proportions were assessed using χ^2 tests. Analysis of covariance was used to evaluate differences in continuous variables at 4 months, adjusting for baseline values, reported as mean with 95% CIs. Multivariable linear regression was used to investigate associations between continuous variables and treatment, and to adjust for potential confounders.

Linear mixed-effects models were used to evaluate the trajectories of variables over time. These models included time and an interaction with study treatment as fixed effects (population-level estimates) and allowed for participant-specific variation in baseline levels and changes (a so-called random slope, random intercept model). Linear, cubic, and quadratic time transformations were considered; best fit for the fixed effects structure was selected based on akaike criterion information (AIC) and bayesian criterion information (BIC) (measures for model fit; lower is better), while the best random effects structure was evaluated via likelihood ratio tests in nested models. The interaction between treatment and time indicates whether a different trajectory (slope) exists between the two treatment groups. All reported p values are two-sided, and a p value of <0.05 was considered significant. All analyses were performed using R: A Language and Environment for Statistical Computing, V.3.02 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

At baseline, HbA1c measurements were available in all but 6 (1.6%) patients. Of these 373 patients, 27 (7.2%) had an HbA1c of $\geq 6.5\%$ (48 mmol/mol; 12 in the placebo group and 15 in the metformin group) and

excluded for the current analysis, resulting in 346 patients without diabetes.

The baseline characteristics of the patients for both groups (metformin group, n=172; placebo group, n=174) are presented in table 1. Both groups were comparable at baseline regarding age, sex, cardiovascular risk profile, cardiovascular history, physical diagnostic measurements, and baseline markers reflective of renal function, glycometabolism, and cholesterol profile.

HbA1c concentration

At 4 months, HbA1c levels in the metformin group were slightly lower than in the placebo group, adjusting for baseline values (table 2). The mean absolute change in HbA1c concentration from baseline to 4 months was 0.06 (95% CI 0.03 to 0.10%); 0.66 mmol/mol (95% CI 0.33 to 1.09) in the metformin group and 0.12% (95% CI 0.08% to 0.15%); 1.31 mmol/mol (95% CI 0.87 to 1.64) in the placebo group (p=0.049; figure 1A). Figure 2 shows the change in HbA1c levels over time in both groups, fitted using a smoothed spline. A linear mixed-effects model evaluating change in HbA1c over time showed a significant interaction between time and study treatment (p=0.031), indicating different trajectories between the metformin and placebo group (figure 2).

Fasting glucose and postchallenge glucose

All patients underwent an OGTT during hospitalization whereas 28 patients (7.5%) refused an OGTT at 4 months (10 patients (5.7%) in the metformin group and 18 patients (10.5%) in the placebo group).

During hospitalization for STEMI, the metformin and placebo group had similar fasting glucose levels (6.4 \pm 1.0 vs 6.4 \pm 0.9 mmol/L, p=0.75), whereas the 120 min postchallenge glucose levels were lower in the metformin group compared with placebo (10.0 \pm 2.7 vs 10.6 \pm 2.5 mmol/L; p=0.03; figure 3A). Four months after STEMI and after stopping the study medication for at least 5 days, there were no differences between the metformin and placebo group concerning the fasting glucose levels (5.6 \pm 0.6 vs 5.6 \pm 0.7 mmol/L, p=0.76) and the 120 min postchallenge glucose levels (7.7 \pm 2.2 vs 7.8 \pm 2.2 mmol/L, p=0.83; figure 3B).

Insulin levels

Twenty-four hours after PCI, the non-fasting insulin level in the metformin group was 34.5 mU/L (95% CI 29.3 to 39.6) and 33.2 mU/L (28.4 to 38.1) in the placebo group (p=0.274). The mean absolute change in insulin levels from baseline to 24 h was 9.2 mU/L (95% CI 4.0 to 14.3) in the metformin group and 7.9 mU/L (95% CI 3.1 to 12.8) in the placebo group (p=0.914). Also at 4 months, insulin levels in the metformin group did not differ from the placebo group, adjusting for baseline values (table 2). The mean absolute change in insulin levels from baseline to 4 months was -3.3 mU/L (95% CI -8.64 to 2.0) in the metformin group and -7.5 mU/L (95% CI -12.6 to -2.4) in the placebo group (p=0.979; figure 1B).

Table 1 Baseline characteristics

Variable	Total (n=346)	Metformin (n=172)	Control (n=174)	p Value
Age, mean (SD), years	58.1±11.7	58.1±11.9	58.2±11.6	0.968
Female sex, N (%)	87 (25)	40 (23)	47 (27)	0.496
Race or ethnic group, N (%)				0.567
Caucasian	335 (97)	168 (98)	167 (96)	
Asian	7 (2.0)	3 (1.7)	4 (2.3)	
Black	4 (1.2)	1 (0.6)	3 (1.7)	
Cardiovascular risk factors, N (%)				
Hypertension	97 (28)	50 (29)	47 (27)	0.759
Dyslipidemia	220 (64)	103 (60)	117 (67)	0.190
Current smoking	190 (55)	96 (56)	94 (54)	0.821
Positive family history	118 (34)	55 (32)	63 (36.2)	0.474
Cardiovascular history				
Stroke	2 (0.6)	1 (0.6)	1 (0.6)	1.000
Previous PCI	4 (1)	1 (0.6)	3 (1.7)	0.623
Physical diagnostics at hospital admission				
Body weight, mean (SD), kg	83.5±14.0	83.6±13.9	83.3±14.1	0.847
Body mass index, mean (SD), kg/m ²	26.7±3.7	26.5±3.5	26.9±3.9	0.401
Systolic blood pressure, mean (SD), mm Hg	134±23	134±22	133±24	0.797
Diastolic blood pressure, mean (SD), mm Hg	84±14	84±14	84±15	0.733
Laboratory values at admission				
Hemoglobin (IQR), mmol/L	8.9±0.8	8.9±0.8	8.9±0.8	0.673
Creatinine (IQR), µmol/L	72 (62–82)	72 (62–84)	73 (63–81)	0.673
Estimated GFR (IQR), mL/min/173 m ²	93±21	93±23	93±19	0.947
Glucose, median (IQR), mmol/L	8.1 (7.0–9.4)	8.1 (7.0–9.2)	8.1 (7.0–9.6)	0.627
HbA1c, median (IQR), %	5.8 (5.6–6.0)	5.7 (5.6–6.0)	5.8 (5.6–6.0)	0.849
HbA1c, median (IQR), mmol/mol	40 (38–42)	39 (38–42)	40 (38–42)	0.849
Insulin, median (IQR), mmol/L	16.9 (9.8–29.2)	18.5 (10.8–30.1)	15.9 (9.3–27.8)	0.169
Total cholesterol (IQR), mmol/L	5.3 (4.8–6.0)	5.3 (4.7–6.1)	5.3 (4.8–6.0)	0.938
LDL-cholesterol (IQR), mmol/L	3.8 (3.2–4.4)	3.7 (3.1–4.5)	3.8 (3.3–4.4)	0.740
HDL-cholesterol (IQR), mmol/L	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	0.821

GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention.

Incidence of diabetes and prediabetes

New-onset diabetes, diagnosed at 4 months, was diagnosed in 20 patients (12%) in the metformin group and 18 patients (10%) in the placebo group ($p=0.70$). Prediabetes was diagnosed in the metformin group in 108 patients (63%) and in 123 patients (71%) in the placebo group ($p=0.40$) after 4 months.

Body weight and BMI

Four months after STEMI, body weight and subsequently BMI were lower in the metformin group compared with placebo (table 2). The patients in the metformin group did not gain weight (0.0 kg (95% CI -0.84 to 0.90)), whereas the weight gain in the control group was 1.4 kg (95% CI 0.56 to 2.3; $p=0.024$; figure 1C). As a consequence, the BMI at 4 months was lower in the metformin group than in the placebo group (table 2). Another important factor possibly influencing body weight is cessation of smoking. The number of smokers at baseline did not differ between groups (table 1). At 4 months, there was no between-group difference in cessation of smoking: 52 patients in the metformin

group had quit smoking versus 63 patients in the placebo group ($p=0.39$).

Total, LDL, and HDL cholesterol

The adjusted total cholesterol levels and LDL cholesterol levels in the metformin group were lower than the placebo group after 4 months (table 2). The mean reduction from baseline to 4 months in total cholesterol in the metformin group was 1.58 mmol/L (95% CI 1.45 to 1.70) and in the placebo group 1.40 mmol/L (95% CI 1.29 to 1.52; $p=0.045$; figure 1D), whereas the mean reduction in LDL-cholesterol was 1.74 mmol/L (95% CI 1.64 to 1.84) in the metformin group and 1.54 mmol/L (95% CI 1.44 to 1.64) in the placebo group ($p=0.007$; figure 1E). The adjusted HDL-cholesterol level did not differ among groups. The mean increase in HDL-cholesterol from baseline to 4 months was 0.04 mmol/L (95% CI 0.01 to 0.07) in the metformin group and 0.07 mmol/L (95% CI 0.04 to 0.10) in the placebo group ($p=0.153$; figure 1F). At baseline, only two patients in the metformin group and three patients in the placebo group had a LDL-cholesterol level of <1.9 mmol/L/L, which is the targeted level for

Table 2 Measurements of glycometabolic state and cardiovascular risk profile at 4 months

Variable	Metformin (n=172)	Control (n=174)	p Value
Physical diagnostics			
Body weight, mean (95% CI), kg	83.8 (83.0 to 84.7)	85.2 (84.4 to 86.1)	0.024
Body mass index, mean (95% CI), kg/m ²	26.8 (26.5 to 27.0)	27.2 (27.0 to 27.5)	0.014
Systolic blood pressure, mean (95% CI), mmHg	123 (120 to 125)	125 (122 to 127)	0.241
Diastolic blood pressure, mean (95% CI), mmHg	74 (72 to 75)	74 (72 to 75)	0.649
Laboratory values			
HbA1c, mean (95% CI), %	5.83 (5.79 to 5.87)	5.89 (5.85 to 5.92)	0.049
HbA1c, mean (95% CI), mmol/mol	40.2 (39.8 to 40.6)	40.9 (40.4 to 41.2)	0.049
Insulin, mean (95% CI), mU/L	22.8 (17.5 to 28.1)	18.6 (13.5 to 23.7)	0.211
Total cholesterol, mean (95% CI), mmol/L	3.85 (3.73 to 3.97)	4.02 (3.90 to 4.14)	0.045
LDL cholesterol, mean (95% CI), mmol/L	2.10 (1.99 to 2.20)	2.30 (2.20 to 2.40)	0.007
HDL cholesterol, mean (95% CI), mmol/L	1.20 (1.16 to 1.23)	1.23 (1.20 to 1.26)	0.153

Values were calculated using ANCOVA, adjusted for baseline variables.

ANCOVA, analysis of covariance; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

cholesterol-lowering therapy.¹ Despite overall lowering LDL values, 49 patients in the metformin versus 46 patients in the placebo group reached the LDL-cholesterol target level of <1.9 mmol/L (p=0.397)

at 4 months. The statins used, and the equipotency of these statins did not differ between groups, since at baseline 12 patients in the metformin group versus 13 patients in the placebo group used statins, and at

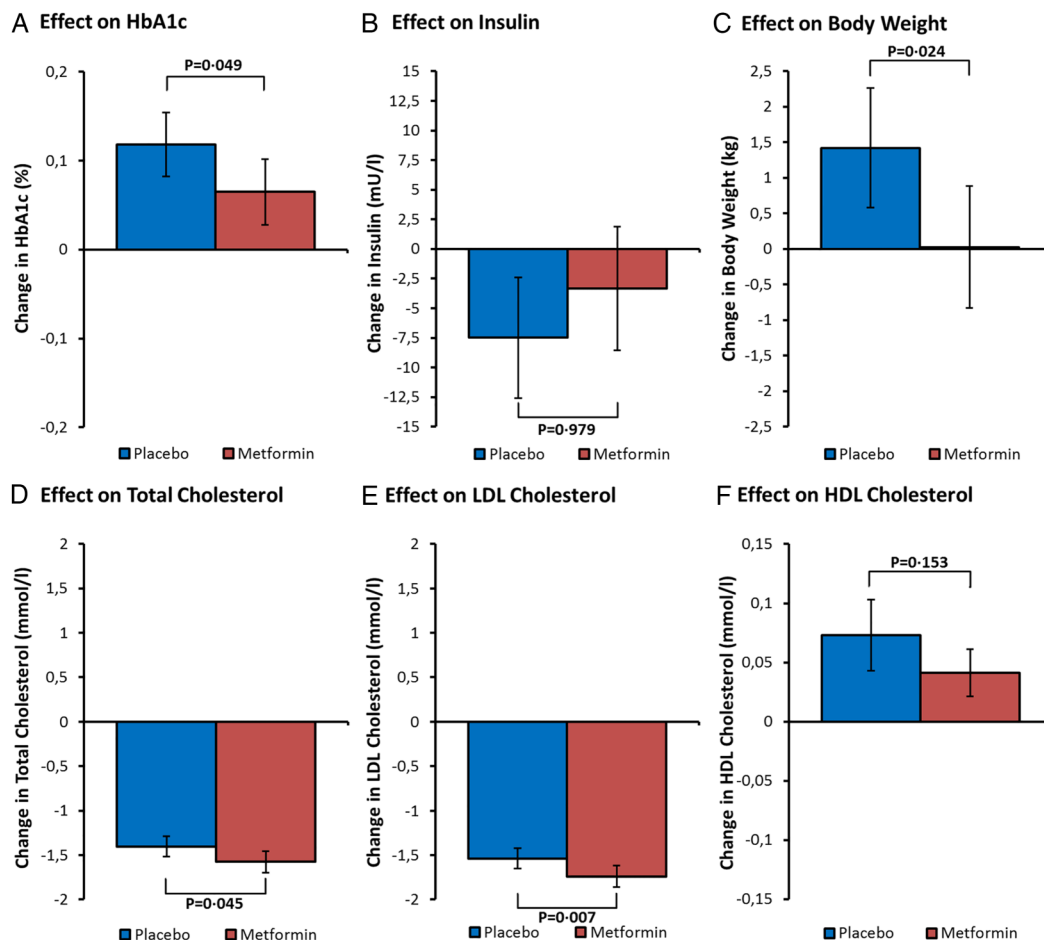
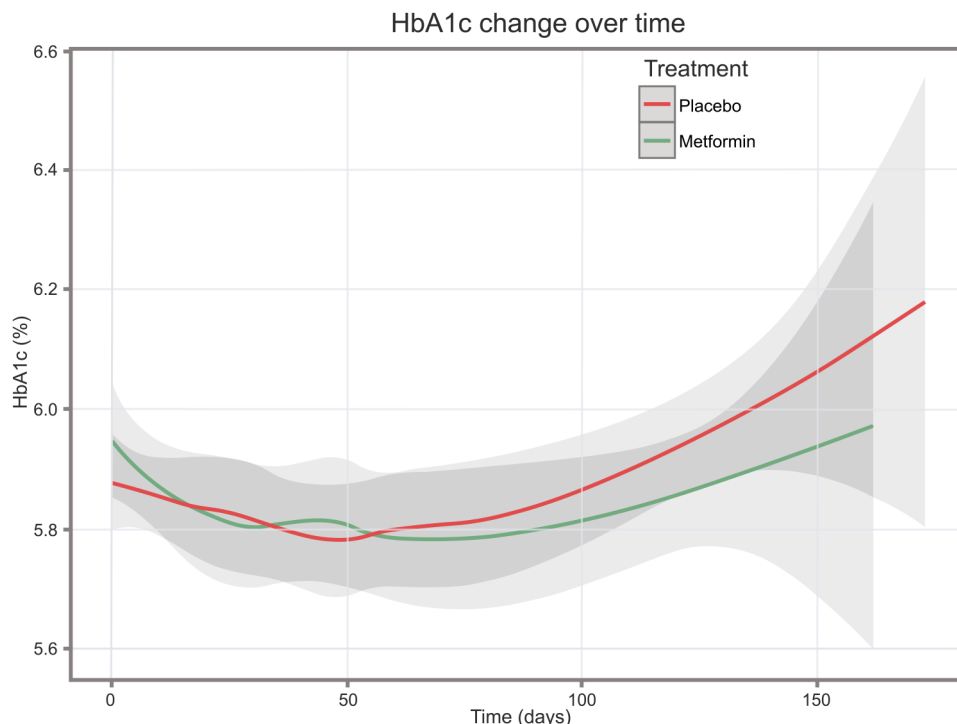


Figure 1 Change in markers of glycometabolism and cardiovascular risk profile. Absolute changes in (95% CI) the metformin and placebo groups in glycated hemoglobin (HbA1c) concentration (A), insulin levels (B), body weight (C), total cholesterol (D), low-density lipoprotein (LDL)-cholesterol (E), and high-density lipoprotein (HDL)-cholesterol (F) were analyzed using analysis of covariance.

Figure 2 Change in glycated hemoglobin (HbA1c) over time. Trajectories of change in HbA1c over time (95% CI) were analyzed using linear mixed-effects model, showing different trajectories between the two treatment groups ($p=0.031$).



4 months 153 vs 157 patients used statins (p =not significant for both time points). At hospital discharge, the statins used and equipotency did not differ (see online supplementary appendix, tables S1 and S2).

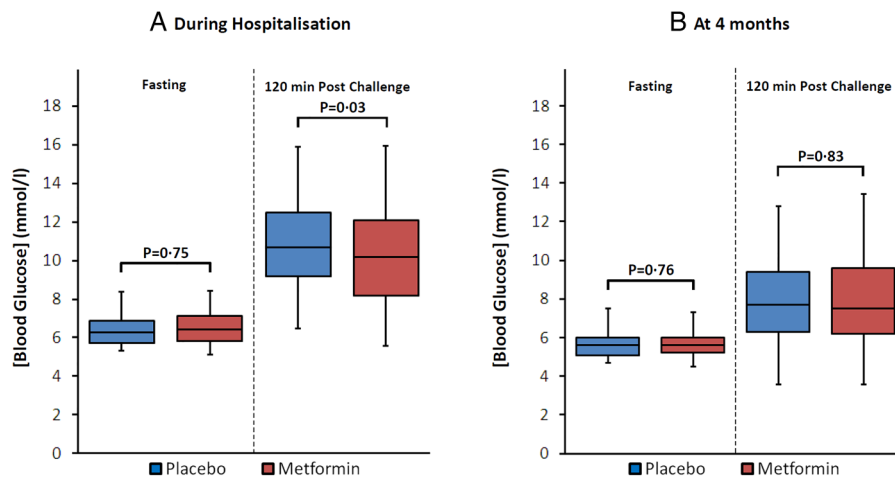
Blood pressure

The systolic and diastolic blood pressure at 4 months was similar in both treatment groups: 123 mm Hg (95% CI 120 to 125) and 74 mm Hg (95% CI 72 to 75) in the metformin group, and 125 mm Hg (95% CI 122 to 127) and 74 mm Hg (95% CI 72 to 75) in the placebo group ($p=0.241$ and $p=0.649$, respectively). The mean decrease in either systolic or diastolic blood pressure from baseline to 4 months did not differ between groups (data not shown).

DISCUSSION

The main observation of this prespecified analysis from the GIPS-III trial is that metformin treatment in patients with STEMI for 4 months on top of standard care leads to a modestly improved cardiovascular risk profile compared with placebo in a subselection of patients without diabetes. HbA1c levels, weight gain, total cholesterol, and LDL-cholesterol levels were all lower in patients receiving metformin. A reduction in the incidence of new-onset diabetes was not observed. Furthermore, systolic and diastolic blood pressure, insulin levels, and HDL cholesterol levels remained unchanged by metformin treatment. These results imply that metformin might be able to modestly reduce the cardiovascular risk in patients without diabetes on top of standard care

Figure 3 Oral glucose tolerance testing during hospitalization and at 4 months after infarction. Bar and whisker plots demonstrating blood glucose concentrations during hospitalization (A) and at 4 months (B). Each plot shows fasting blood glucose concentration left of the dotted line, and 120 min postchallenge glucose concentration right of the dotted line. The bars represent median (p_{50}) and IQR (p_{25} and p_{75}) and the whiskers p_5 and p_{95} .



(including statin therapy). Whether these findings are substantial and can lead to a reduction in cardiovascular events remains to be determined.

Our results concerning HbA1c levels are comparable with results from the recent Carotid Atherosclerosis: METformin for insulin ResistAnce (CAMERA) study, that demonstrated that 18 months of treatment with metformin in patients with coronary artery disease without diabetes also resulted in a reduction of HbA1c levels.¹⁹ The Diabetes Prevention Program (DPP) demonstrated that 3 years of treatment with metformin 850 mg twice daily significantly lowered HbA1c in comparison to placebo.¹³ The DPP study demonstrated that metformin treatment at long-term follow-up resulted in a reduction in the development of diabetes.¹⁴ In all three studies (DPP, CAMERA, and the GIPS-III), the observed effect of metformin treatment on HbA1c was significant yet small. The use of markers of HbA1c as a prognostic marker is not unequivocal.²⁵ However, the incremental prognostic value of HbA1c on top of standard risk factors has been established.²⁶ Therefore, it is generally accepted that lowering HbA1c likely is associated with improved prognosis. Still, the clinical relevance of metformin-induced lowering of HbA1c on the incidence and risk of future major cardiac events remains to be determined.

During hospitalization, one to maximally four dosages of metformin treatment already resulted in a lower post-challenge blood glucose concentrations compared with placebo. Since we did not measure fasting insulin levels 24 h after PCI, this effect could be due to directly lowering insulin resistance, but also due to other glucose-lowering effects of metformin, such as reduction of hepatic gluconeogenesis may be of effect. Hyperglycemia is often present during and the days following myocardial infarction, and is associated with impaired myocardial reperfusion, larger myocardial infarct size, and impaired outcome.³ Therefore, many studies using insulin-based strategies have aimed at lowering glucose levels during myocardial infarction.^{27–29} However, none of those trials showed improved outcome, yet all of those trials concluded that lowering insulin resistance was achieved and associated with improved outcome. Regrettably, the insulin-based therapies instituted increased risk of hypoglycemia and mortality, resulting in an overall adverse effect. Our analysis suggests that metformin can lower glucose levels during STEMI, without the adverse effects of insulin-based lowering strategies. Whether administration of metformin prior to reperfusion, with adequate blood levels of metformin, in patients with STEMI (for instance in the ambulance) will result in improved outcome, cannot be deduced from this trial.

Another very interesting and important observation in our study was that metformin prevented weight gain. The overall weight gain after STEMI (in GIPS-III this was 1.4 kg in the placebo group) is likely due to inactivity after myocardial infarction. There was no difference in the number of patients who stopped smoking after STEMI between

both groups, suggesting that cessation of smoking did not affect these results. The DPP study group calculated that 64% of the effect of metformin treatment on cardiovascular risk reduction was caused by weight reduction.³⁰ Fontbonne *et al*²⁰ demonstrated in The BIGuanides and Prevention of Risks in Obesity (BIGPRO1) study that metformin treatment (850 mg twice daily) for 1 year resulted a weight reduction of 1.2 kg compared with placebo. In support of this, Preiss *et al*¹⁹ demonstrated in the CAMERA study that metformin treatment for 18 months resulted in a mean weight loss of 3.2 kg compared with placebo. So, if weight reduction is one of the targets for improvement of cardiovascular risk, metformin should be considered as an addendum to achieve this.

Our study demonstrated that metformin effectively lowers LDL cholesterol and total cholesterol levels on top of initiation of statin therapy. The BIGPRO1 study showed that metformin treatment for 1 year resulted in a reduction of 0.16 mmol/L in total cholesterol and 0.12 mmol/L in LDL-cholesterol.²⁰ However, these patients were not treated with statins or other lipid-lowering drugs. In contrast, Preiss *et al*¹⁹ did not report an effect of 18 months of metformin treatment on cholesterol levels in patients without diabetes with coronary artery disease in the CAMERA study. One of the eligibility criteria in the CAMERA study was statin therapy, which all patients received already for 6.5 years on average. In our study, only 25 of 346 (7.2%) of patients used statins since the STEMI mostly was their first presentation with cardiovascular disease, but at hospital discharge 99.5% of patients in our study received statins.²² Second, the total cholesterol levels at baseline in the CAMERA were much lower than in our trial (4.3 vs 5.3 mmol/L). Third, the average reduction in cholesterol level at 6 months was 0.03 mmol/L in the CAMERA trial, whereas in our trial on average a reduction of 1.4 mmol/L was observed, with a larger reduction in the metformin group compared with the placebo group. Since the effect of metformin lowering total cholesterol and LDL on top of statin therapy was clearly visible in our study, metformin may exert cholesterol-lowering qualities during initiation of treatment.

This prespecified substudy of the GIPS-III trial had several strengths. The GIPS-III had a double-blind, placebo-controlled trial, and included patients at the same time point in their illness, namely directly after PCI for STEMI. All end points were adjudicated by an independent end point committee. The dosages of metformin used (500 mg bid) are commonly used to treat type 2 diabetes mellitus. A potential weakness of the GIPS-III trial was that it was not designed for mortality reduction through secondary prevention of the cardiovascular risk profile. However, several clinically relevant and targeted markers were lowered by metformin therapy, suggesting the sample size is sufficient to address cardiovascular risk profile. The study medication was only administered for 4 months, which in terms of secondary prevention is short.

Altogether, we observed that metformin treatment in patients without diabetes presenting with STEMI, resulted in prevention of gain in body weight, improved levels of HbA1c, and improved levels of LDL and total cholesterol. Estimating the total effect size on cardiovascular risk of these combined effects is difficult. A risk calculator for outcome after STEMI, integrating all important known variables, has yet to be developed. However, quantification of the effect sizes on outcome is necessary in order to establish the usefulness and benefit of metformin in secondary prevention. Therefore, further study on the effects of metformin on cardiovascular risk profile and prognosis in patients with STEMI are warranted. Currently, the Glucose Lowering in Non-diabetic hyperglycemia Trial (GLINT, ISRCTN34875079) is an ongoing double-blind, randomized controlled trial set to include over 12 000 patients designed to assess the effect of metformin in non-diabetic hyperglycemia on cardiovascular risk.

CONCLUSION

In patients with acute myocardial infarction at risk for diabetes, 4 months of treatment with metformin on top of optimal treatment resulted in a modestly more favorable cardiovascular risk profile compared with placebo. Metformin treatment improved glycemic control and cholesterol levels, and prevented gain in body weight. Whether these favorable effects on risk factors can be translated to improved long-term outcomes requires further study.

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REFERENCES

1. Steg PG, James SK, Atar D, *et al.*, Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569–619.
2. Timmer JR, Ottervanger JP, de Boer MJ, *et al.* Primary percutaneous coronary intervention compared with fibrinolysis for myocardial infarction in diabetes mellitus: results from the Primary Coronary Angioplasty vs Thrombolysis-2 trial. *Arch Intern Med* 2007;167:1353–9.
3. van der Horst IC, Nijsten MW, Vogelzang M, *et al.* Persistent hyperglycemia is an independent predictor of outcome in acute myocardial infarction. *Cardiovasc Diabetol* 2007;6:2.
4. Timmer JR, van der Horst IC, Ottervanger JP, *et al.* Zwolle Myocardial Infarction Study Group. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. *Am Heart J* 2004;148:399–404.
5. Timmer JR, Hoekstra M, Nijsten MW, *et al.* Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention. *Circulation* 2011;124:704–11.
6. Norhammar A, Tenerz A, Nilsson G, *et al.* Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002;359:2140–4.
7. Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;55:1577–96.
8. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–65.
9. Holman RR, Paul SK, Bethel MA, *et al.* 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–89.
10. Mellbin LG, Malmberg K, Norhammar A, *et al.* DIGAMI 2 Investigators. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J* 2008;29:166–76.
11. Mellbin LG, Malmberg K, Norhammar A, *et al.* DIGAMI 2 Investigators. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. *Diabetologia* 2011;54:1308–17.
12. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–53.
13. Knowler WC, Barrett-Connor E, Fowler SE, *et al.*, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.
14. Orchard TJ, Temprosa M, Barrett-Connor E, *et al.* Diabetes Prevention Program Outcomes Study Research Group. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. *Diabet Med* 2013;30:4655.

15. Ramachandran A, Snehalatha C, Mary S, *et al.* Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006;49:289–97.
16. Yang W, Liu J, Shan Z, *et al.* Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial. *Lancet Diabetes Endocrinol* 2014;2:46–55.
17. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2012;35:731–7.
18. Johnson JA, Simpson SH, Toth EL, *et al.* Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. *Diabet Med* 2005;22:497–502.
19. Preiss D, Lloyd SM, Ford I, *et al.* Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. *Lancet Diabetes Endocrinol* 2014;2:116–24.
20. Fontbonne A, Charles MA, Juhan-Vague I, *et al.*, BIGPRO Study Group. The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. *Diabetes Care* 1996;19:920–6.
21. The Diabetes Prevention Program Research Group. Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: effects of lifestyle intervention and metformin. *Diabetes* 2005;54:2404–14.
22. Lexis CP, van der Horst IC, Lipsic E, *et al.*, GIPS-III Investigators. Effect of metformin on left ventricular function after acute myocardial infarction in patients without diabetes: the GIPS-III randomized clinical trial. *JAMA* 2014;311:1526–35.
23. Lexis CP, van der Horst IC, Lipsic E, *et al.*, GIPS-III Investigators. Metformin in non-diabetic patients presenting with ST elevation myocardial infarction: rationale and design of the glycometabolic intervention as adjunct to primary percutaneous intervention in ST elevation myocardial infarction (GIPS)-III trial. *Cardiovasc Drugs Ther* 2012;26:417–26.
24. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care* 2014;37:S14–80.
25. Rydén L, Grant PJ, Anker SD, *et al.* ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;34:3035–87.
26. Di Angelantonio E, Gao P, Khan H, *et al.*, for The Emerging Risk Factors Collaboration. Glycated hemoglobin measurement and prediction of cardiovascular disease. *JAMA* 2014;311:1225–33.
27. van der Horst IC, Zijlstra F, van 't Hof AW, *et al.*, Zwolle Infarct Study Group. Glucose-insulin-potassium infusion inpatients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomized trial. *J Am Coll Cardiol* 2003;42:784–91.
28. Malmberg K, Rydén L, Wedel H, *et al.*, DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;26:650–61.
29. Díaz R, Goyal A, Mehta SR, *et al.* Glucose-insulin-potassium therapy in patients with ST-segment elevation myocardial infarction. *JAMA* 2007;298:2399–405.
30. The Diabetes Prevention Program Research Group. Factors associated with diabetes onset during metformin versus placebo therapy in the Diabetes Prevention Program. *Diabetes* 2007;56:1153–9.