Metformin and preservation of left ventricular function

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CHAPTER 7
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.

Submitted

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ABSTRACT

Objective:
In patients with diabetes mellitus, metformin treatment is associated with reduced mortality and attenuation of cardiovascular risk. We evaluated whether metformin treatment in STEMI patients without diabetes improves the cardiovascular risk profile.

Methods:
A total of 380 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 to placebo (n=174); HbA1c (5.83% [95 CI 5.79–5.87%] vs. 5.89% [95% CI 5.85–5.92%]) (40.2 mmol/mol [95% CI 39.8–40.6 mmol/mol vs. 40.9 mmol/mol [95% CI 40.4–41.2 mmol/mol, P=0.049]), total cholesterol (3.85 mmol/L [95% CI 3.73–3.97 mmol/L] vs. 4.02 mmol/L [95% CI 3.90–4.14 mmol/L], P=0.045), LDL-cholesterol (2.10 mmol/L [95% CI 1.99–2.00 mmol/L]) vs. 2.3 mmol/L [95% CI 2.20–2.40 mmol/L], P=0.007), body weight (83.8 kg [95% CI 83.0–84.7 kg] vs. 85.2 kg [95% CI 84.4–86.1 kg], P=0.024), BMI (26.8 kg/m2 [95% CI 26.5–27.0 kg/m2] vs. 27.2 kg/m2 [95% CI 27.0–27.5 kg/m2], P=0.014). Levels of fasting glucose, post-challenge glucose, insulin, HDL-cholesterol, and blood pressure were similar both groups.

Conclusion:
Among patients with STEMI without diabetes, treatment with metformin for 4 months resulted in a more favorable cardiovascular risk profile compared to placebo.
INTRODUCTION

After ST-segment elevation myocardial infarction (STEMI) secondary prevention therapies as recommended by current guidelines such as beta-blockers, angiotensin-converting enzyme inhibitors, platelet aggregation inhibitors (acetylsalicylic acid and others), and lipid lowering drugs all have been proven to reduce mortality and attenuate cardiovascular risk profile. In addition to the targeted substrates by current therapies, such as blood pressure, neuroendocrine activation, and increased thrombogenity, glycometabolic dysregulation is strongly associated with adverse outcome after STEMI. Impaired fasting glucose and insulin resistance is associated with impaired prognosis, even at levels of dysglycemia not yet diagnostic of diabetes mellitus. Dysglycemia is common in STEMI patients – as much as one in every four patients have undiagnosed diabetes and up to one in every two patients has prediabetes. 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. Metformin has been shown to improve cardiovascular outcome, with a benefit that exceeds the benefit that may be expected solely by blood glucose lowering. In patients with diabetes mellitus and cardiovascular disease, metformin was associated with reduced all-cause mortality compared to other antihyperglycemic strategies. 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. Further, in patients at risk for diabetes, but without cardiovascular disease, metformin reduced diabetes development with 30–40%. We aimed to evaluate if metformin treatment, on top of standard care, would improve cardiovascular risk in non-diabetic patients. 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 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) trial have been reported previously.\textsuperscript{21,22} 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 1 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 an HbA1c of $\geq 6.5\%$ [48 mmol/mol] prior to admission), 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.\textsuperscript{21,22} 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, glycated hemoglobin (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 AM and 08:59 PM were subjected to a standardized oral glucose tolerance test (OGTT) with 75 g of glucose (dissolved in 200 mL water) the following morning.23 In patients arriving at the CCU between 09:00 PM and 23:59 PM, 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 counselling on diet, smoking, and lifestyle and were offered a cardiac rehabilitation program.1,24 Patients who were diagnosed with new onset diabetes were seen by an endocrinologist.

Patients visited the outpatient clinic two weeks, seven weeks and four months after discharge. At four months, a standardized OGTT was performed after an overnight fast of at least eight hours. In order to assess whether the study medication actually affected underlying dysglycemia rather than masking its presence, the OGTT was scheduled at least three 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, post-challenge glucose, insulin levels, cholesterol levels, body weight, BMI, and blood pressure at four 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 degrees Celsius on a chemoluminescence immuno assay (Architect i2000 SR Immunoassay analyser, 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 ≥6.5% (48 mmol/mol), and/or a fasting blood glucose of ≥7.0 mmol/L and/or a 2-h post-challenge 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 minutes post-challenge blood glucose 7.8–11.0 mmol/L; patients not meeting any of these criteria were classified as normoglycemic.\(^{23}\)

**Statistical analyses**

Continuous variables are reported as means±SD or medians [interquartile range, IQR] for normally and non-normally distributed data, respectively. Differences between groups were tested using Student’s t-test or ANOVA for normally distributed data, and Wilcoxon or Kruskall-Wallis tests for non-normally distributed data. Differences in proportions were assessed using chi-squared tests. ANCOVA was used to evaluate differences in continuous variables at 4 months, adjusting for baseline values, reported as mean with 95% Confidence Intervals (CI). 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 subject-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 AIC and 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, version 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 ≥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 four 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 four months was 0.06 (95% CI 0.03–0.10%) [0.66 mmol/mol (95% CI 0.33–1.09 mmol/mol)] in the metformin group and 0.12% (95% CI 0.08–0.15%) [1.31 mmol/mol (95% CI 0.87–1.64 mmol/mol)] 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 post challenge glucose
All patients underwent an OGTT during hospitalization whereas 28 patients (7.5%) refused an OGTT at four 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±1.0 mmol/L vs. 6.4±0.9 mmol/L, P=0.75), whereas the 120 minutes post challenge glucose levels were lower in the metformin group compared to placebo (10.0±2.7 mmol/L, vs. 10.6±2.5 mmol/L; P=0.03) (Figure 3A). Four months after STEMI and after stopping the study medication for at least five days, there were no differences between the
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Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=346)</th>
<th>Metformin (n=172)</th>
<th>Control (n=174)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>58±11±7.7</td>
<td>58±11±1.9</td>
<td>58±2±11.6</td>
<td>0.968</td>
</tr>
<tr>
<td>Female sex – No. (%)</td>
<td>87 (25)</td>
<td>40 (23)</td>
<td>47 (27)</td>
<td>0.496</td>
</tr>
<tr>
<td>Race or ethnic group – No. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.567</td>
</tr>
<tr>
<td>Caucasian</td>
<td>335 (97)</td>
<td>168 (98)</td>
<td>167 (96)</td>
<td>?</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (2.0)</td>
<td>3 (1.7)</td>
<td>4 (2.3)</td>
<td>?</td>
</tr>
<tr>
<td>Black</td>
<td>4 (1.2)</td>
<td>1 (0.6)</td>
<td>3 (1.7)</td>
<td>?</td>
</tr>
<tr>
<td>Cardiovascular Risk Factors – No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>97 (28)</td>
<td>50 (29)</td>
<td>47 (27)</td>
<td>0.759</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>220 (64)</td>
<td>103 (60)</td>
<td>117 (67)</td>
<td>0.190</td>
</tr>
<tr>
<td>Current smoking</td>
<td>190 (55)</td>
<td>96 (56)</td>
<td>94 (54)</td>
<td>0.821</td>
</tr>
<tr>
<td>Positive family history</td>
<td>118 (34)</td>
<td>55 (32)</td>
<td>63 (36.2)</td>
<td>0.474</td>
</tr>
<tr>
<td>Cardiovascular History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>4 (1)</td>
<td>1 (0.6)</td>
<td>3 (1.7)</td>
<td>0.623</td>
</tr>
<tr>
<td>Physical diagnostics at hospital admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, mean (SD), kg</td>
<td>83±5±14.0</td>
<td>83.6±13.9</td>
<td>83±3±14.1</td>
<td>0.847</td>
</tr>
<tr>
<td>Body-mass Index, mean (SD), kg/m²</td>
<td>26±7±3.7</td>
<td>26±5±3.5</td>
<td>26±9±3.9</td>
<td>0.401</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mmHg</td>
<td>134±23</td>
<td>134±22</td>
<td>133±24</td>
<td>0.797</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mmHg</td>
<td>84±14</td>
<td>84±14</td>
<td>84±15</td>
<td>0.733</td>
</tr>
<tr>
<td>Laboratory values at admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (IQR), mmol/L</td>
<td>8.9±0.8</td>
<td>8.9±0.8</td>
<td>8.9±0.8</td>
<td>0.673</td>
</tr>
<tr>
<td>Creatinine (IQR), μmol/L</td>
<td>72 (62–82)</td>
<td>72 (62–84)</td>
<td>73 (63–81)</td>
<td>0.673</td>
</tr>
<tr>
<td>Estimated GFR (IQR), (mL/min/173m²)</td>
<td>93±21</td>
<td>93±23</td>
<td>93±19</td>
<td>0.947</td>
</tr>
<tr>
<td>Glucose, median (IQR), mmol/L</td>
<td>8.1 (7.0–9.4)</td>
<td>8.1 (7.0–9.2)</td>
<td>8.1 (7.0–9.6)</td>
<td>0.627</td>
</tr>
<tr>
<td>HbA1c, median (IQR), %</td>
<td>5.8 (5.6–6.0)</td>
<td>5.7 (5.6–6.0)</td>
<td>5.8 (5.6–6.0)</td>
<td>0.849</td>
</tr>
<tr>
<td>Insulin, median (IQR), mmol/L</td>
<td>16.9 (9.8–29.2)</td>
<td>18.5 (10.8–30.1)</td>
<td>15.9 (9.3–27.8)</td>
<td>0.169</td>
</tr>
<tr>
<td>HbA1c, median (IQR), mmol/mol</td>
<td>40 (38–42)</td>
<td>39 (38–42)</td>
<td>40 (38–42)</td>
<td>0.849</td>
</tr>
<tr>
<td>Total cholesterol (IQR), mmol/L</td>
<td>5.3 (4.8–6.0)</td>
<td>5.3 (4.7–6.1)</td>
<td>5.3 (4.8–6.0)</td>
<td>0.938</td>
</tr>
<tr>
<td>LDL cholesterol (IQR), mmol/L</td>
<td>3.8 (3.2–4.4)</td>
<td>3.7 (3.1–4.5)</td>
<td>3.8 (3.3–4.4)</td>
<td>0.740</td>
</tr>
<tr>
<td>HDL cholesterol (IQR), mmol/L</td>
<td>1.1 (0.9–1.3)</td>
<td>1.1 (0.9–1.3)</td>
<td>1.1 (0.9–1.3)</td>
<td>0.821</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; PCI, percutaneous coronary intervention; IQR, interquartile range; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; LDL, low density lipoprotein; HDL high density lipoprotein.

metformin and placebo group concerning the fasting glucose levels (5.6±0.6 mmol/L vs. 5.6±0.7 mmol/L, P=0.76) and the 120 minutes post challenge glucose levels (7.7±2.2 mmol/L vs. 7.8±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 34.5mU/L (95% CI 29.3–39.6 mU/L) and 33.2 mU/L (28.4–38.1 mU/L) in the placebo group; (P=0.274). The mean absolute change in insulin
levels from baseline to 24 hours was 9.2 mU/L (95% CI 4.0–14.3 mU/L) in the metformin group and 7.9 mU/L (95% CI 3.1–12.8 mU/L) in the placebo group (P=0.914). Also at four 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 four months was -3.3 mU/L (95% CI -8.64–2.0 mU/L) in the metformin group and -7.5 mU/L (95% CI -12.6–-2.4 mU/L) in the placebo group (P=0.979; Figure 1B).

**Incidence of diabetes and prediabetes**

New-onset diabetes, diagnosed at four 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 four months.

**Body Weight and Body-Mass Index**

Four months after STEMI, body weight and subsequently BMI were lower in the metformin group compared to placebo (Table 2). The patients in the metformin group did not gain weight (0.0 kg (95% CI -0.84–0.90 kg), whereas the weight gain in the control group was 1.4 kg (95% CI 0.56–2.3 kg; P=0.024) (Figure 1C). As a consequence the BMI at four 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, vs. 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 four months (Table
The mean reduction from baseline to four months in total cholesterol in the metformin group was 1.58 mmol/L (95% CI 1.45–1.70 mmol/L) and in the placebo group 1.40 mmol/L (95% CI 1.29–1.52 mmol/L; P=0.045; Figure 1D), whereas the mean reduction in LDL cholesterol was 1.74 mmol/L (95% CI 1.64–1.84 mmol/L) in the metformin group and 1.54 mmol/L (95% CI 1.44–1.64 mmol/L) 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 four months was 0.04 mmol/L (95% CI 0.01–0.07 mmol/L) in the metformin group and 0.07 mmol/L (95% CI 0.04—0.10 mmol/L) in the placebo group (P=0.153; Figure 1F). At baseline only two patients in the metformin group and three patient in the placebo group had a LDL cholesterol level of < 1.9 mmol/L, which is the targeted level for cholesterol lowering therapy.¹ Despite overall lowering LDL values, 49 patients in the metformin vs. 46 patients in the placebo group reached the LDL cholesterol target level of < 1.9 mmol/L (P=0.397) at 4 months. The statin use between groups did not differ, since at baseline 12 patients in the metformin group vs. 13 patients in the placebo group used statins, and at 4 months 153 vs. 157 patients used statins (P=ns for both time points).

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 minutes post challenge glucose concentration right of the dotted line. The bars represent median (p50) and interquartile range (p25 and p75) and the whiskers p5 and p95.
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Blood Pressure
The systolic and diastolic blood pressure at four months was similar in both treatment groups: 123 mmHg (95% CI 120–125 mmHg) and 74 mmHg (95% CI 72–75 mmHg) in the metformin group and 125 mmHg (95% CI 122–127 mmHg) and 74 mmHg (95% CI 72–75 mmHg) 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 four 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 for four months on top of standard care leads to an improved cardiovascular risk profile compared to placebo in STEMI 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 reduce the cardiovascular risk in patients without diabetes on top of standard care (including statin therapy). Whether these findings are substantial and can lead to less cardiovascular events, remains to be determined.

Our result 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. The Diabetes Prevention Program (DPP) demonstrated that 3 years of treatment with metformin 850 mg twice daily significantly lowered HbA1c in comparison to placebo, however their population consisted solely of patients with prediabetes and therefore a more substantial reduction compared to our study population is to be expected. The use of markers of HbA1c as a diagnostic marker is not unequivocal. However, the incremental prognostic value of HbA1c on top of standard risk factors has been established. Therefore, it is generally accepted that
Metformin and cardiovascular risk profile

Lowering HbA1c likely is associated with improved prognosis.

During hospitalization, 1 to maximally 4 dosages of metformin treatment already resulted in a lower post-challenge blood glucose concentrations compared to placebo. Since we did not measure fasting insulin levels 24h 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.²⁶–²⁸ 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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metformin (n=172)</th>
<th>Control (n=174)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical diagnostics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, mean (95% CI), kg</td>
<td>83·8 (83·0–84·7)</td>
<td>85·2 (84·4–86·1)</td>
<td>0·024</td>
</tr>
<tr>
<td>Body-mass Index, mean (95% CI), kg/m²</td>
<td>26·8 (26·5–27·0)</td>
<td>27·2 (27·0–27·5)</td>
<td>0·014</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (95% CI), mmHg</td>
<td>123 (120–125)</td>
<td>125 (122–127)</td>
<td>0·241</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (95% CI), mmHg</td>
<td>74 (72–75)</td>
<td>74 (72–75)</td>
<td>0·649</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c, mean (95% CI), %</td>
<td>5·83 (5·79–5·87)</td>
<td>5·89 (5·85–5·92)</td>
<td>0·049</td>
</tr>
<tr>
<td>HbA1c, mean (95% CI), mmol/mol</td>
<td>40·2 (39·8–40·6)</td>
<td>40·9 (40·4–41·2)</td>
<td>0·049</td>
</tr>
<tr>
<td>Insulin, mean (95% CI), mU/L</td>
<td>22·8 (17·5–28·1)</td>
<td>18·6 (13·5–23·7)</td>
<td>0·211</td>
</tr>
<tr>
<td>Total cholesterol, mean (95% CI), mmol/L</td>
<td>3·85 (3·73–3·97)</td>
<td>4·02 (3·90–4·14)</td>
<td>0·045</td>
</tr>
<tr>
<td>LDL cholesterol, mean (95% CI), mmol/L</td>
<td>2·10 (1·99–2·20)</td>
<td>2·30 (2·20–2·40)</td>
<td>0·007</td>
</tr>
<tr>
<td>HDL cholesterol, mean (95% CI), mmol/L</td>
<td>1·20 (1·16–1·23)</td>
<td>1·23 (1·20–1·26)</td>
<td>0·153</td>
</tr>
</tbody>
</table>

Values were calculated using ANCOVA, adjusted for baseline variables. Abbreviations: SD, standard deviation; IQR, interquartile range; HbA1c, glycated haemoglobin; LDL, low density lipoprotein; HDL high density lipoprotein.
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 STEMI patients (for instance in the ambulance) will result in improved outcome, cannot be deducted 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 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. Fontbonne and colleagues 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 to placebo. In support of this, Preiss and colleagues demonstrated in the CAMERA study that metformin treatment for 18 months resulted in a mean weight loss of 3.2 kg compared to 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 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. However these patients were not treated with statins or other lipid lowering drugs. In contrast, Preiss and colleagues did not report an effect of 18 months of metformin treatment on cholesterol levels in non-diabetic patients 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. Secondly, the total cholesterol levels at baseline in the CAMERA were much lower than in our trial (4.3 mmol/L vs. 5.3 mmol/L). Thirdly, 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 to 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 trough 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 HbA1 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-nondiabetic hyperglycemia on cardiovascular risk.
CONCLUSION

In patients with acute myocardial infarction at risk for diabetes, four months of treatment with metformin on top of optimal treatment resulted in a 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.
References


Chapter 7


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