Metformin in Acute Myocardial Infarction in Patients without Diabetes

Glycometabolic **I**nterventions in **P**atients presenting with **S**T-segment Elevation Myocardial Infarction (GIPS)-III trial

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Disclosures and Funding

Chris P.H. Lexis has no conflicts of interest

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Background (1)

Myocardial infarction in the western world

- 1 in every 7 people dies from consequences of MI
  - Late or early
- 1-year mortality 10 – 15%

Left ventricular dysfunction after MI

- in 30 – 50% of patients
- heart failure in 20 – 40%
- the strongest predictor of outcome after STEMI

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Steg PG, et al. ESC Guidelines for the management of STEMI. Eur Heart J, 2012.

Background (2)

Metformin

- The most widely used oral antihyperglycemic drug
- In top 20 prescription drugs

Metformin in patients with diabetes (UKPDS):

- 36% reduction of all cause mortality
- 42% diabetes related death
- 32% any diabetes related endpoint

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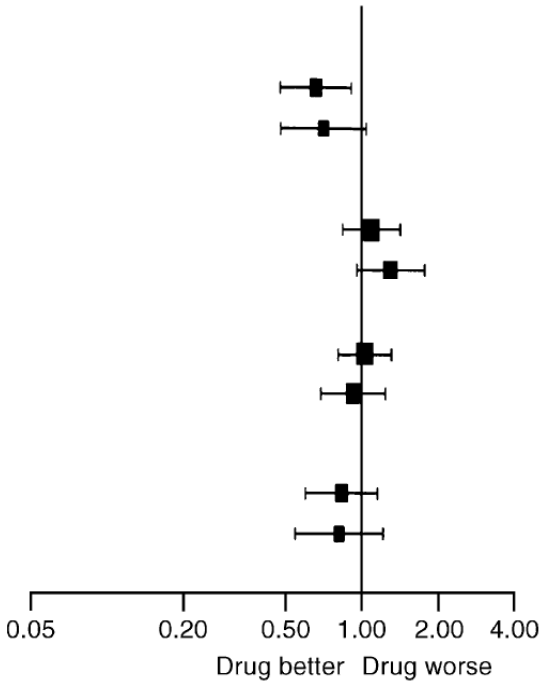
UK Prospective Diabetes Study (UKPDS) Group. Lancet, 1998.

Background (3)

The DIGAMI 2 trial (n=1253) in patients with DM and MI

- Metformin HR 0.65 (0.47–0.90) for death

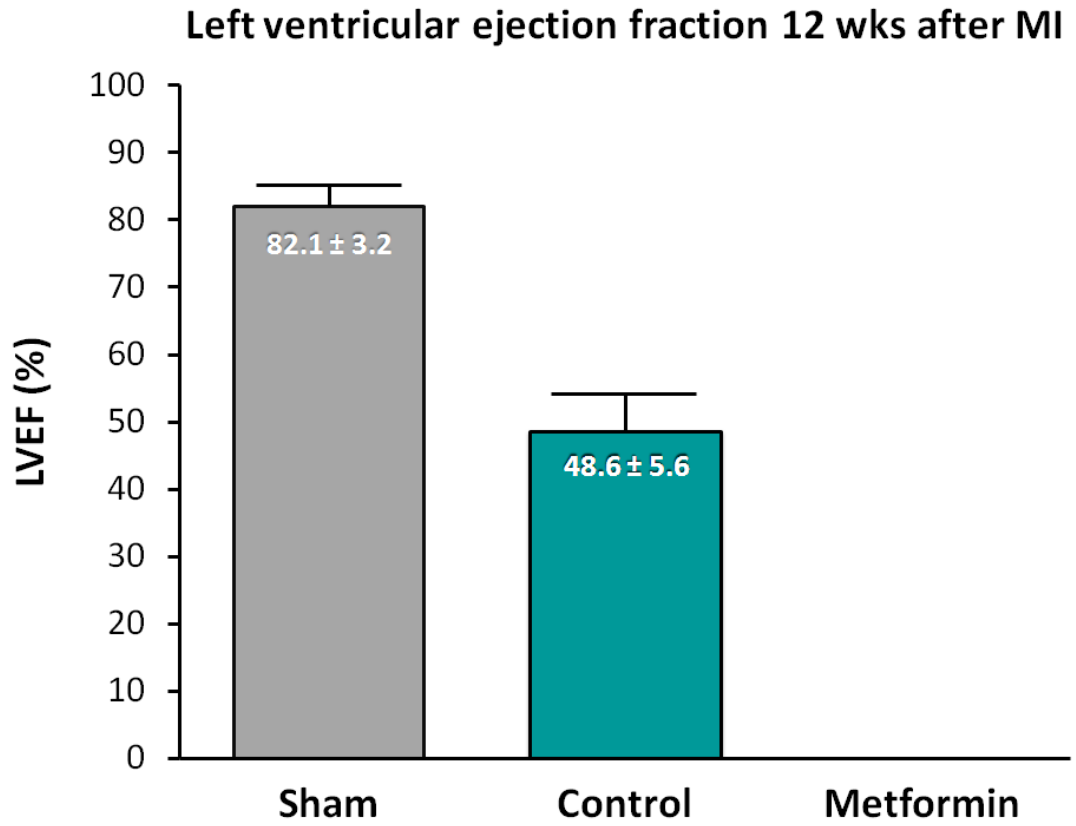
	Hazard ratio (95 % CI)	*p*-value
Metformin (185/888)[a]		
Death (47/271)[b]	0.65 (0.47–0.90)	0.0094
CV death (31/176)[b]	0.72 (0.49–1.06)	0.0995
Sulfonylurea (250/823)[a]		
Death (79/239)[b]	1.09 (0.84–1.42)	0.5251
CV death (57/152)[b]	1.29 (0.94–1.76)	0.1145
Insulin (631/442)[a]		
Death (208/110)[b]	1.03 (0.80–1.31)	0.8312
CV death (133/74)[b]	0.90 (0.67–1.21)	0.4726
Any glucose-lowering drug (912/161)[a]		
Death (276/42)[b]	0.83 (0.60–1.16)	0.2737
CV death (181/26)[b]	0.79 (0.53–1.17)	0.2398



Mellbin L, et al. Diabetologia, 2011.

Background (4)

Animal experimental (rats) of myocardial infarction



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Yin MM, et al. Am J Physiol Heart Circ Physiol, 2011;
Lexis CP, et al. Cardiovasc Drug Ther, 2012.

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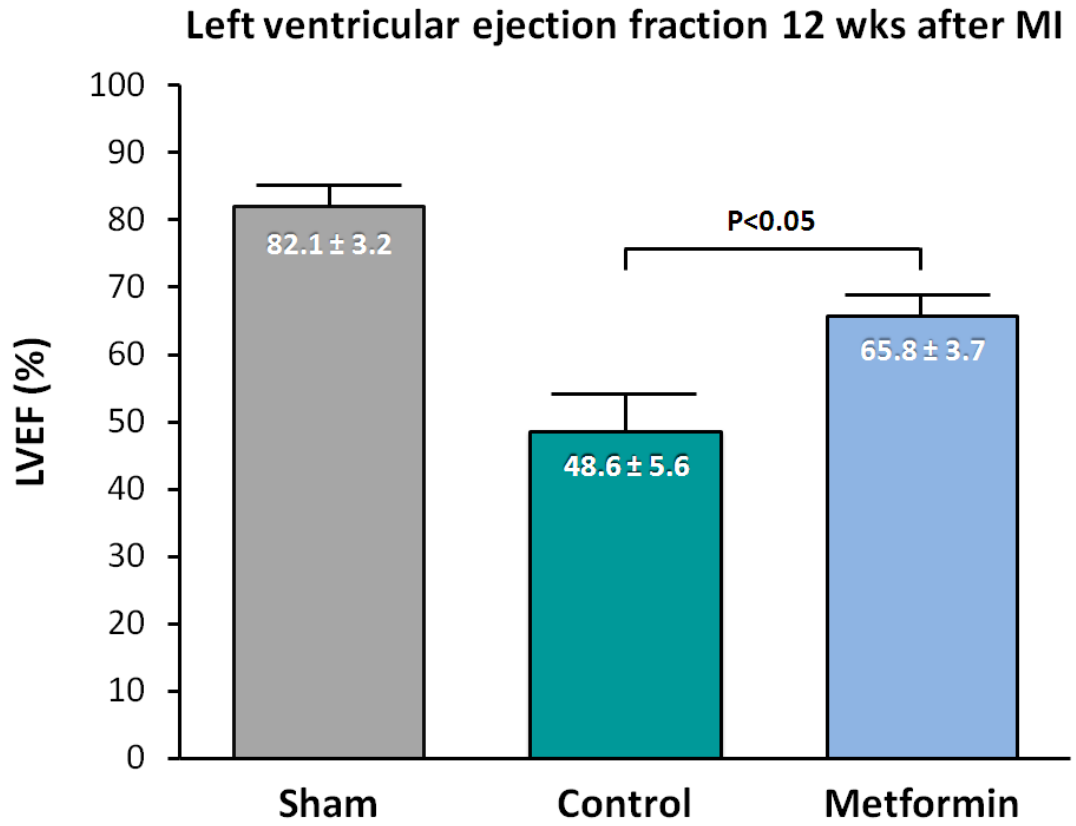

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Yin MM, et al. Am J Physiol Heart Circ Physiol, 2011;
Lexis CP, et al. Cardiovasc Drug Ther, 2012.

Objective

To study the effect of metformin on left ventricular function in patients without DM presenting with STEMI

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Design and intervention

GIPS-III trial

- Double blind
- Randomized 1:1
- Placebo controlled
- Parallel group

Intervention

- Metformin 500 mg twice daily vs placebo twice daily
- Started immediately after PCI
- Continued for 4 months

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Lexis CP, et al. Cardiovasc Drug Ther, 2012.

Endpoints

Primary endpoint

- Left ventricular ejection fraction (LVEF)
- 4 months after myocardial infarction
- Measured by 3.0 Tesla MRI
  - Independent core laboratory
  - Blinded to allocation

Secondary endpoints

- Concentration of NT-proBNP at 4 months
- Clinical events
- Safety parameters
- Glycometabolic state

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Sample size

Based on LVEF by MRI

- 80% power to detect a difference in LVEF 3% (SD 9%)
- 141 patients with evaluable MRI per group
- Allow for 25% dropout
- Total sample size 380 patients

Statistical Analyses

- according to a predefined Statistical Analysis Plan

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Eligibility

Inclusion criteria

- Patients aged >18 years with STEMI
- Primary PCI with ≥ 1 stent of 3.0 mm in diameter
- TIMI flow grade post PCI ≥ 2

Key exclusion criteria

- Diabetes
- Prior MI
- Need for cardiothoracic surgery
- Contraindication for MRI
- Severe renal impairment

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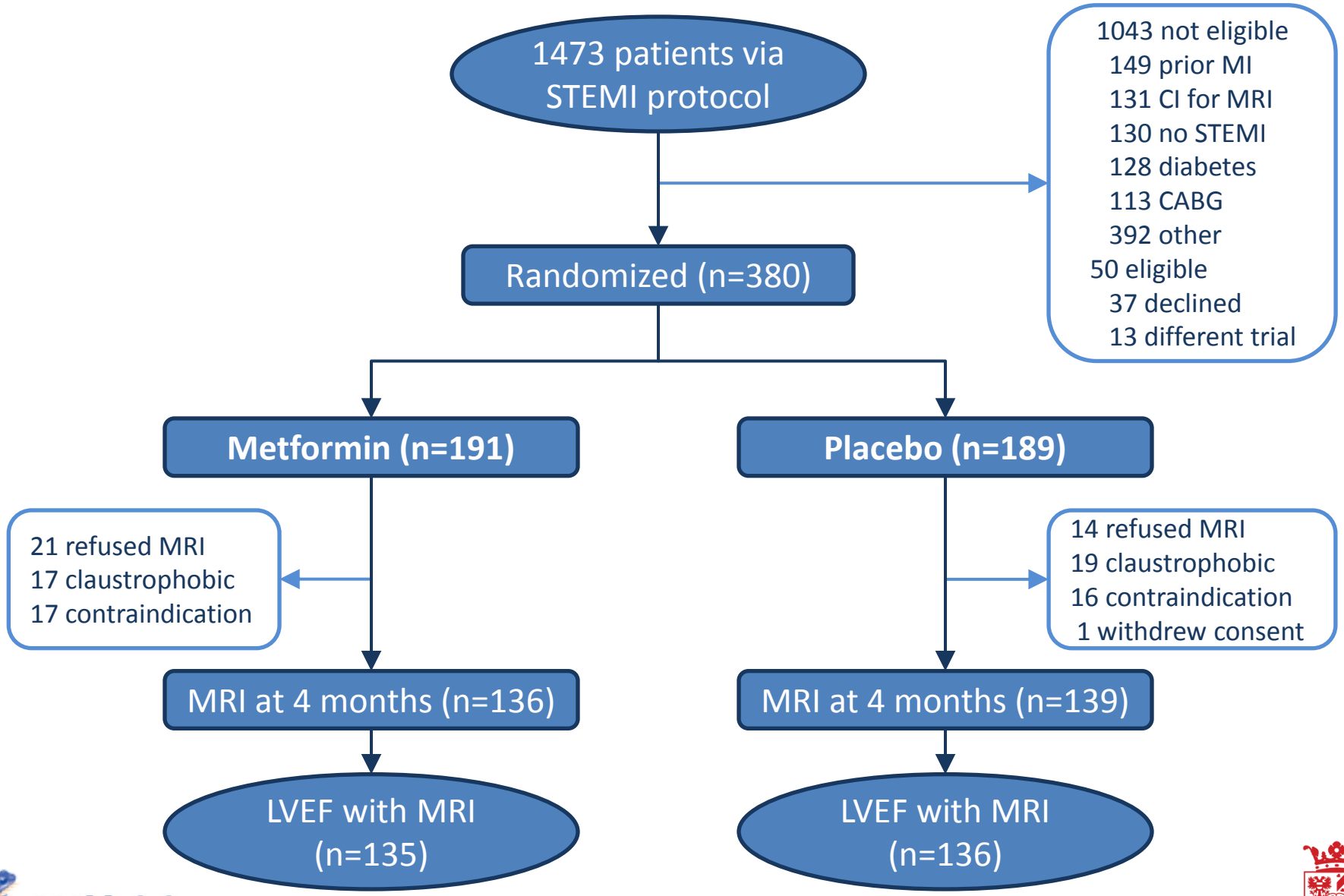
Patient Flow



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Baseline Characteristics (1)

	Metformin (n=191)	Placebo (n=188)
Age – years	58.7	58.8
Female sex – %	24.6	25.5
BMI – kg/m^2	26.9	27.0
Hypertension – %	31.9	27.1
Dyslipidemia – %	58.1	68.1
Current smoker – %	56.5	53.7
Previous PCI – %	0.5	1.6
Stroke – %	1.1	0.5
Systolic blood pressure – mmHg	134	134
Diastolic blood pressure – mmHg	84	84
Heart rate – beats/min	75	77
Ischemia time – min	171	153

Baseline Characteristics (2)

	Metformin (n=191)	Placebo (n=188)
Angiographic characteristics		
Anterior infarction – %	39.3	37.8
TIMI flow grade pre PCI ≤ 1 – %	59.1	64.9
TIMI flow grade post PCI < 3 – %	12.6	5.3
Myocardial blush grade ≤ 1 – %	13.8	5.9
Laboratory markers at admission		
CK – U/L	133	123
CKMB – U/L	16	16
Creatinine – µmol/L	71	72
NT-proBNP – ng/L	83	79
Glucose – mmol/L	8.2	8.4
HbA1c – %	5.8	5.8

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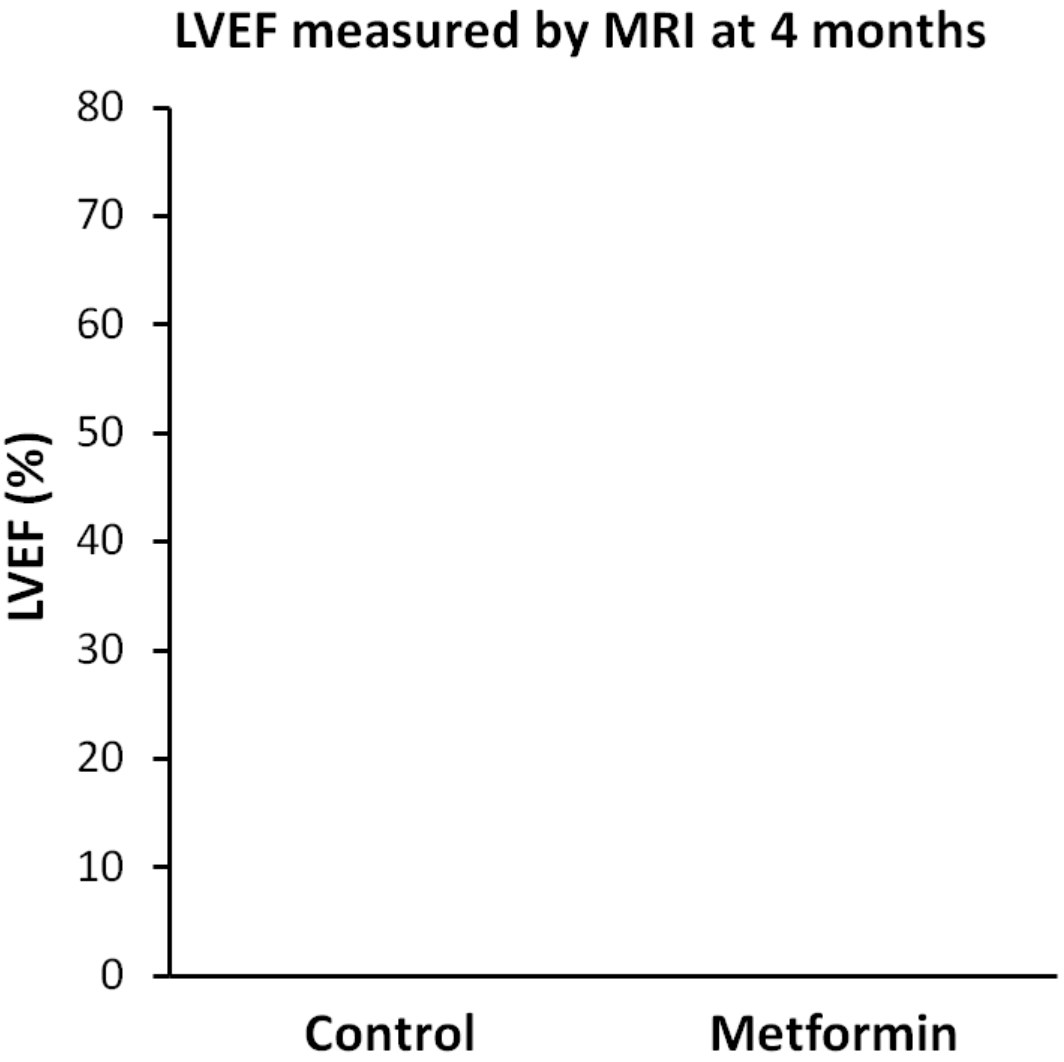
Primary Endpoint



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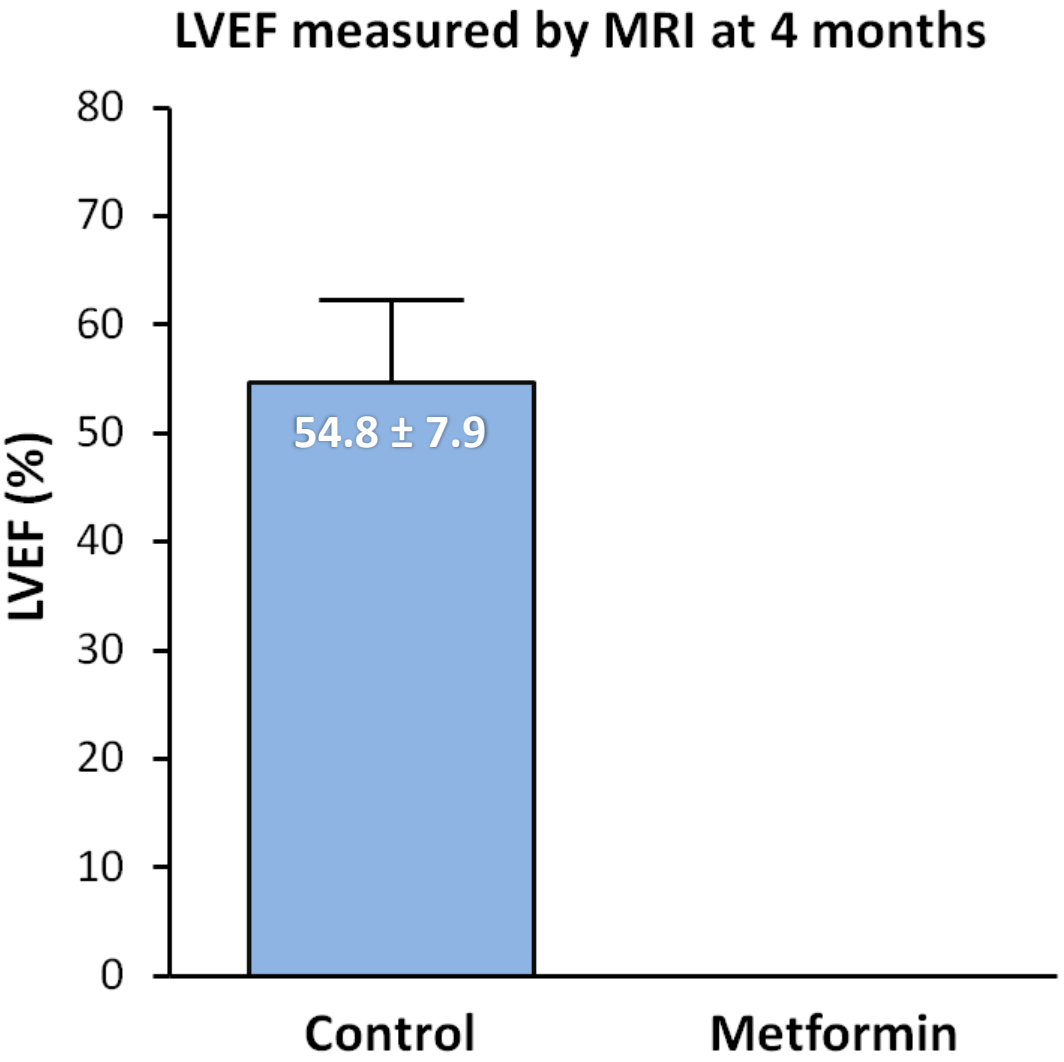

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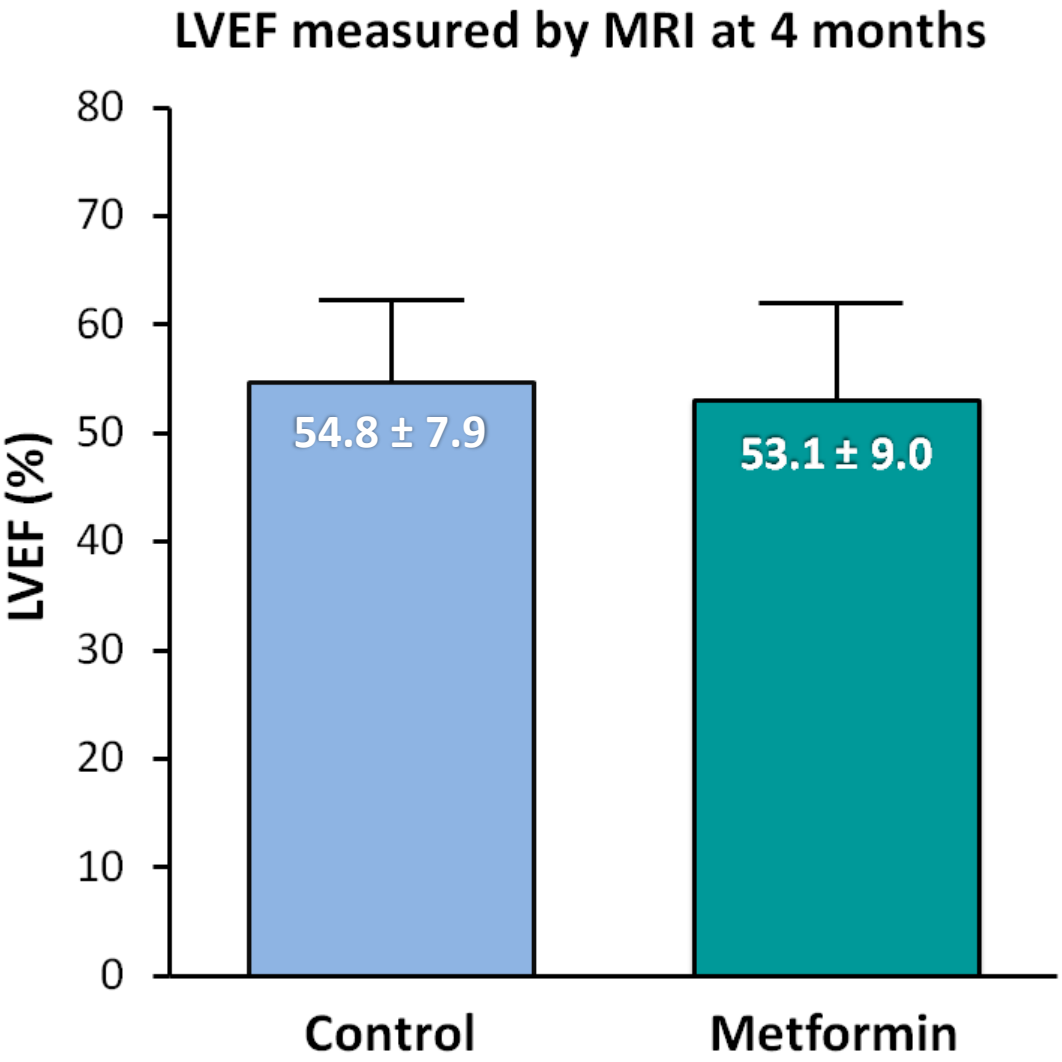

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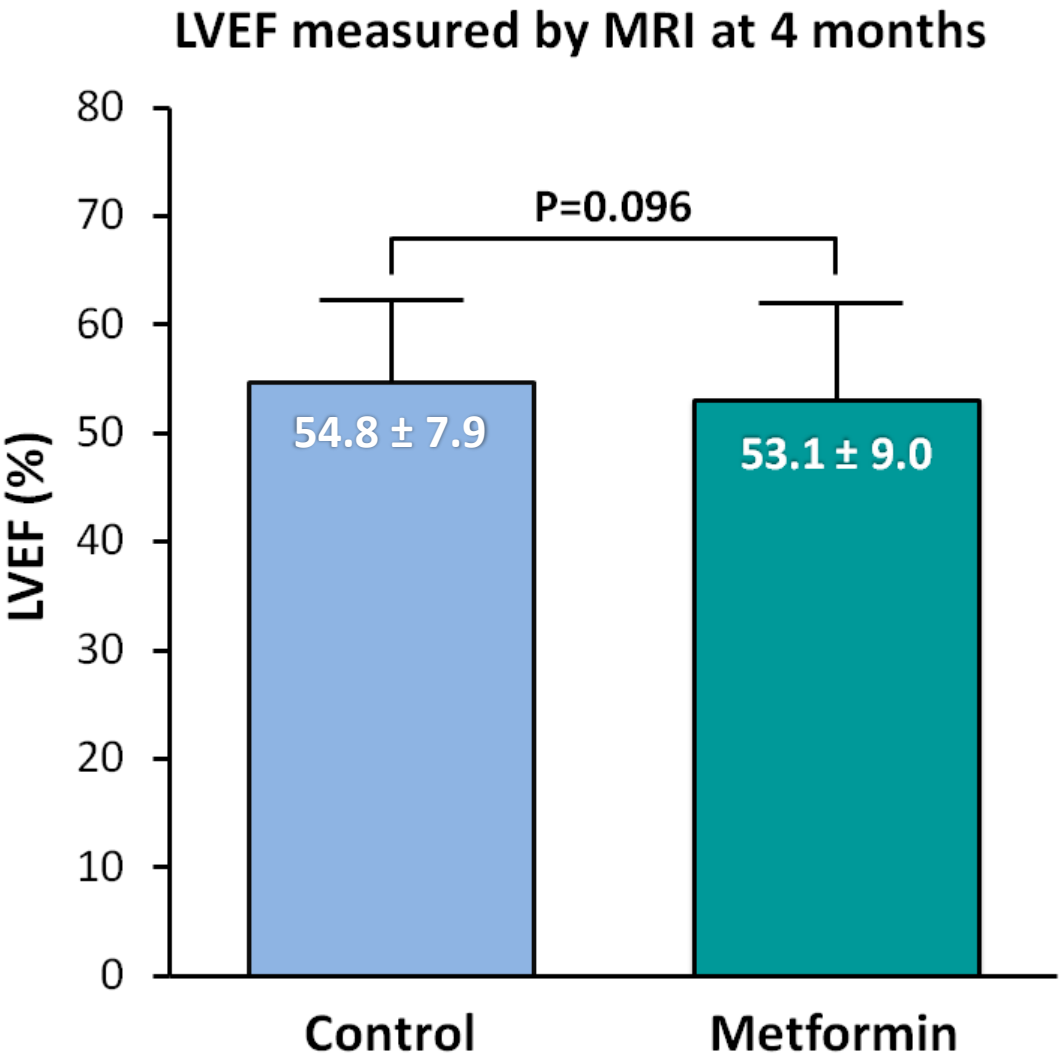
Primary Endpoint



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Endpoints

	Metformin group	Placebo group	*P*-value
Primary endpoint			
LVEF ± SD – %	53.1 ± 9.0	54.8 ± 7.9	0.096
Principal secondary endpoint			
Laboratory markers at 4 months			

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NT-proBNP at 4 mo (IQR) – ng/L	167 (65 – 393)	167 (74 – 383)	0.66
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NT-proBNP at 4 mo (IQR) – ng/L	167 (65 – 393)	167 (74 – 383)	0.66
Laboratory markers at 4 months			
Creatinine (IQR) – µmol/L	79 (70 – 87)	79 (72 – 89)	0.61
Glucose (IQR) – mmol/L	5.7 (5.2 – 6.3)	5.6 (5.2 – 6.2)	0.96
HbA1c (IQR) – %	5.9 (5.6 – 6.1)	5.9 (5.7 – 6.1)	0.15

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Events at 4 months

	Metformin (n=191)	Placebo (n=188)	*P*-value
Death – no.	0	0	
Death, reinfarction or target lesion revascularization – no.	6	2	0.16
Reinfarction – no.	5	2	0.26
STEMI – no.	1	1	0.99
Non-STEMI – no.	4	1	0.18
Stent Thrombosis – no.	2	1	0.57
Ischemia driven reintervention – no.	8	7	0.82
Target lesion revascularization – no.	3	1	0.33
Hospitalization for heart failure – no.	2	0	0.16
Diabetes – no.	32	27	0.56

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Adverse events

	Metformin (n=191)	Placebo (n=188)	*P*-value
Discontinuation of study medication due to adverse events – no.	6	4	0.751
Severe renal impairment – no. (eGFR < 30ml/min)	0	0	
Lactic acidosis – no.	0	0	
Gastro-intestinal complaints – no.	35	21	0.060
Nausea – no.	10	2	0.036
Diarrhoea – no.	3	1	0.623
Gastric/abdominal pain – no.	13	13	1.000
Obstipation – no.	5	0	0.061
Decreased appetite – no.	3	0	0.248

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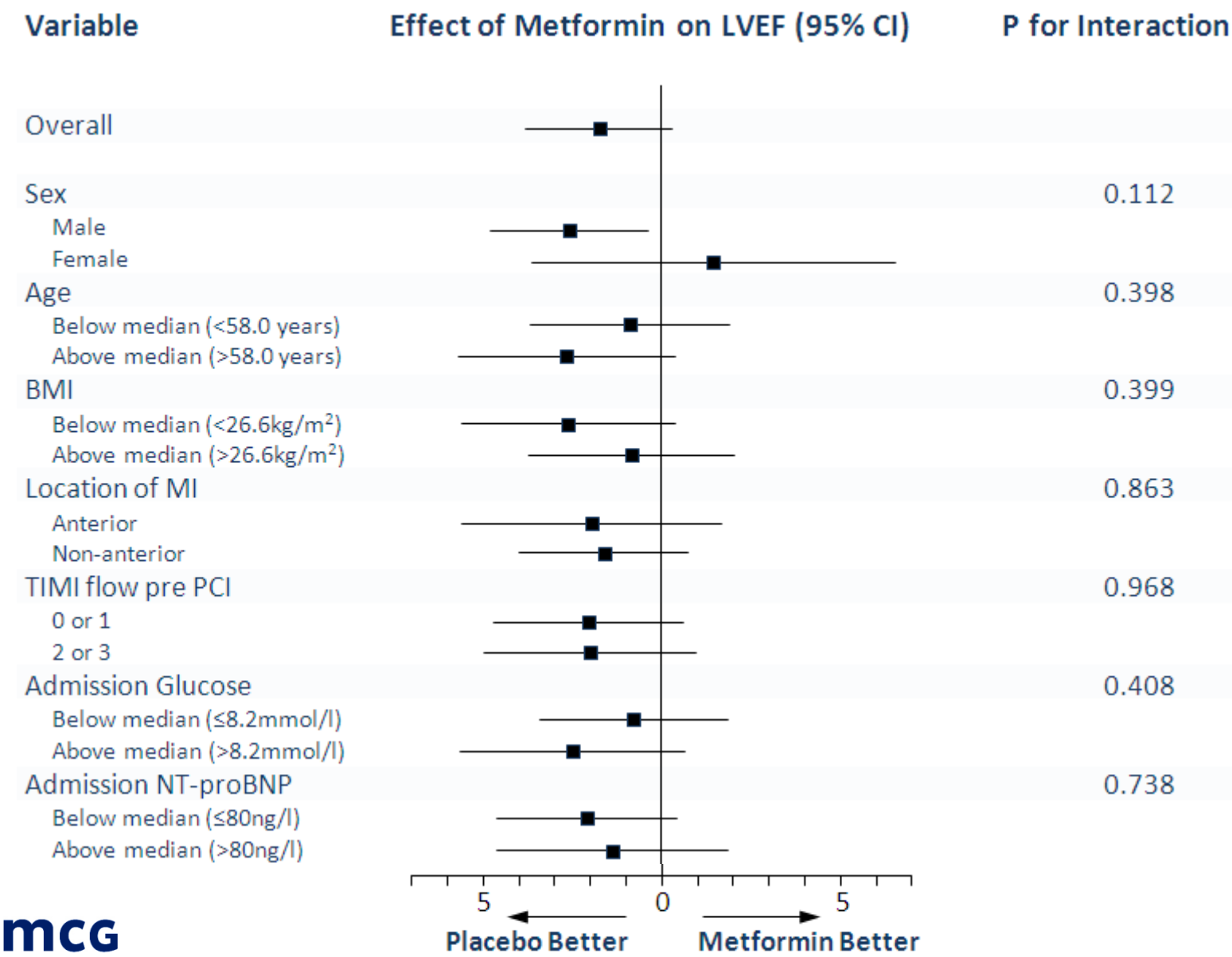
Prespecified Subgroups



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Conclusion

- In patients without diabetes, metformin 500mg 2dd, started directly after PCI and continued for 4 months does not preserve left ventricular ejection fraction after STEMI as compared to placebo

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Conclusion

- In patients without diabetes, metformin 500mg 2dd, started directly after PCI and continued for 4 months does not preserve left ventricular ejection fraction after STEMI as compared to placebo

- Metformin is safe to use after STEMI

- The current results do not support the use of metformin in this setting

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- Rudolf A. de Boer
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- Bruce H.R. Wolffenbuttel

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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 µmol/L [IQR, 70-87 µmol/L] vs 79 µmol/L [IQR, 72-89 µmol/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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Author Affiliations: Author affiliations are listed at the end of this article.

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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