

Supplementary Online Content

Lexis CPH, van der Horst ICC, Lipsic E, et al; for the 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*. doi: 10.1001/jama.2014.3315

eMethods 1. GIPS-III Committees and Investigators

eMethods 2. Definitions of Clinical End Points

eTable 1. Medical Therapy at Hospital Discharge

eTable 2. Baseline Characteristics of the Population That Underwent Primary End Point

eTable 3. Comparison of Baseline Characteristics by Primary End Point Assessment

eTable 4. Clinical Outcomes at 4 Months by Primary End Point Assessment

This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods 2. Definitions of Clinical End Points

Death

Mortality will be divided into cardiac and non-cardiac. Cardiac death will be divided into three categories: heart failure, sudden death and other. A cardiologist will confirm deaths from cardiovascular causes by examining medical records obtained from hospitals and attending physicians or from attending general practitioner if the patient died at home. Sudden cardiac death will be defined as either witnessed, or un-witnessed, cardiac arrest without evidence of circulatory collapse, such as hypotension, exacerbation of congestive heart failure, or altered mental status, before the disappearance of the pulse or abrupt collapse occurring within one hour of the onset of the symptoms that resulted in death. Death due to heart failure will be defined as death due to clinically end-stage heart failure during hospital admission or by exacerbation of congestive heart failure reported by an attending general practitioner. For all these deaths, no probable non-cardiac cause should be suggested by the history or autopsy.

Reinfarction

Any case of new infarction occurring after the index percutaneous coronary intervention (PCI) procedure will be regarded as a recurrent myocardial infarction. In all cases of recurrent myocardial infarction, troponin T or I may be used for the diagnosis of new myocardial infarction in the absence of CK-MB at the discretion of the Endpoint Adjudication Committee taking into consideration all available clinical and laboratory evidence of new myocardial infarction. A recurrent myocardial infarction is either classified as STEMI or Non-STEMI. Each myocardial infarction, regardless of being classified as STEMI or Non-STEMI, can also be classified as Stent Thrombosis. As a reference for these definitions the consensus criteria as proposed by Cutlip et al, (Circulation, 2007) were used.

Recurrent STEMI is defined as:

- recurrent signs and symptoms of ischemia at rest, accompanied by new or recurrent ST-segment elevations of at least 0.1 mV in at least two contiguous leads lasting at least 30 minutes, and;
- typical rise and fall of biochemical markers of myocardial necrosis (including troponin, CK-MB, CK) to above the upper limit of normal (or if markers already elevated, greater than 50% of the lowest recovery enzyme level from the index infarction).

Recurrent Non-STEMI is defined as:

- recurrent signs and symptoms of ischemia at rest, accompanied by new or recurrent ST-segment elevations not meeting criteria for STEMI lasting at least 30 minutes, and;
- typical rise and fall of biochemical markers of myocardial necrosis (including troponin, CK-MB, CK) to above the upper limit of normal (or if markers already elevated, greater than 50% of the lowest recovery enzyme level from the index infarction).

Stent Thrombosis is defined as:

- confirmation of stent thrombosis by angiography with either an occlusive or non-occlusive thrombus, and;
- pathological confirmation of recent thrombus after autopsy or visual confirmation of recent thrombus after thrombectomy, and;
- acute onset of ischemic symptoms at rest or new ischemic ECG changes that suggest acute ischemia or typical rise and fall of biochemical markers of myocardial necrosis (including troponin,

CK-MB, CK) to above the upper limit of normal (or if markers already elevated, greater than 50% of the lowest recovery enzyme level from the index infarction).

Recurrent coronary interventions

As a reference for these definitions the consensus criteria as proposed by Cutlip et al, (Circulation, 2007) were used.

Recurrent coronary interventions will be classified as being either ischemia-driven interventions (including myocardial infarctions) or interventions solely based on baseline, pre-study treatment, angiography and clinical information.

Target lesion revascularization was defined as:

- new therapeutic percutaneous coronary intervention (PCI) after the index procedure, in the same coronary segment (defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent) treated during the index procedure.

Target vessel revascularization was defined as:

- new therapeutic percutaneous coronary intervention (PCI) after the index procedure, in the same coronary artery (which includes upstream and downstream branches), but not in the same coronary segment (defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent) treated during the index procedure.

Non-target vessel revascularization was defined as:

- new therapeutic percutaneous coronary intervention (PCI) after the index procedure, in a different coronary artery treated during the index procedure.

Coronary artery bypass grafting was defined as:

- new therapeutic coronary artery bypass grafting (CABG) after the index procedure.

Stroke

Stroke is defined as the presence of a new focal neurologic deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours. Stroke is further classified as ischemic, hemorrhagic or type uncertain.

Hospitalization for heart failure

The following definition is used to classify hospitalization for heart failure:

- an overnight stay after discharge from the index event with different dates of admission and discharge, and;
- signs and symptoms consistent with heart failure, confirmed by clinical findings and laboratory parameters, and;
- no alternative clinical explanation for the signs and symptoms.

Hospitalization for chest pain

The following definition is used to classify hospitalization for chest pain:

- an overnight stay after discharge from the index event with different dates of admission and discharge, and;
- recurrent signs and symptoms of suggestive of ischemia, and;
- absence of new or recurrent ST-segment elevations or depression suggestive of MI, and;
- no rise of biochemical markers of myocardial necrosis (including troponin, CK-MB, CK) to above the upper limit of normal (or if markers already elevated, greater than 50% of the lowest recovery enzyme level from the index infarction), and;
- no alternative clinical explanation for the signs and symptoms.

Internal Cardiac Defibrillator implantation

The following definition is used to classify Internal Cardiac Defibrillator (ICD) implantation:

- implantation of an ICD after the index event.

Lactic Acidosis

The following definition is used to classify lactic acidosis:

- acidosis (pH<7.35), and;
- lactate levels >5mmol/l.

eTable 1. Medical Therapy at Hospital Discharge

Drug Category	Total (n=379)	Metformin (n=191)	Control (n=188)	P Value
Aspirin, No. (%)	367 (96.8)	184 (96.3)	183 (97.3)	0.58
Acenocoumarol, No. (%)	20 (5.3)	13 (6.8)	7 (3.7)	0.18
Thienopyridines – No. (%)	379 (100)	191 (100)	188 (100)	1.00
Clopidogrel	271 (71.5)	135 (70.7)	136 (72.0)	0.82
Prasugrel	4 (1.1)	1 (0.5)	3 (1.6)	0.37
Ticagrelor	105 (27.7)	55 (28.8)	50 (26.5)	0.65
ACE-inhibitor or ARB, No. (%)	301 (79.4)	158 (82.7)	143 (76.1)	0.11
Beta-blocker, No. (%)	363 (95.8)	179 (93.7)	184 (97.4)	0.14
Calcium-channel blocker, No. (%)	12 (3.2)	9 (4.7)	3 (1.6)	0.083
Aldosteron-recept antagonist, No. (%)	38 (10.0)	25 (13.1)	13 (6.9)	0.045
Diuretic, No. (%)	12 (3.2)	8 (4.2)	4 (2.1)	0.25
Statin, No. (%)	377 (99.5)	190 (99.5)	187 (99.5)	0.99
Insulin, No. (%)	5 (1.3)	4 (2.1)	1 (0.5)	0.18
Oral antihyperglycemic agent, No. (%)	5 (1.3)	2 (0.5)	3 (1.6)	0.31

ACE, angiotensin converting enzyme; ARB, angiotension-receptor blocker. Medical therapy at hospital discharge for either discharge home, or transfer to a referring hospital.

eTable 2. Baseline Characteristics of the Population That Underwent Primary End Point

Characteristic	Total (n=271)	Metformin (n=135)	Control (n=136)
Age, mean (SD), years	57.7±11.6)	57.6±11.7	57.8±11.5
Female sex – No. (%)	58 (21.4)	28 (20.7)	30 (22.1)
Body-mass Index, mean (SD), kg/m ²	26.9±3.5	26.9±3.7	26.9±3.3
Race or ethnic group – No. (%)			
Caucasian	257 (94.8)	129 (95.6)	128 (94.1)
Asian	10 (3.7)	5 (3.7)	5 (3.7)
Black	4 (1.5)	1 (0.7)	3 (2.2)
Cardiovascular related history – No. (%)			
Hypertension	75 (27.7)	41 (30.4)	34 (25.0)
Dyslipidemia	168 (62.0)	77 (57.0)	91 (66.9)
Current smoking	139 (51.3)	73 (54.1)	66 (48.5)
Stroke	1 (0.4)	1 (0.7)	0
Peripheral artery disease	0	0	0
Previous PCI	4 (1.5)	1 (0.7)	3 (2.2)
Blood pressure, mean (SD), mmHg			
Systolic	132±22	133±21	132±23
Diastolic	84±15	85±15	83±15
Heart rate, mean (SD), beats/min	76±16	76±15	76±16
Ischemia time, median (IQR), min	155 (105–240)	163 (109–266)	147 (102–221)
Single vessel disease – No. (%)	195 (72.0)	93 (68.9)	102 (75)
Infarct-related artery – No. (%)			
Left main	0	0	0
Left anterior descending coronary artery	111 (41.0)	55 (40.7)	56 (41.2)
Left circumflex coronary artery	46 (17.0)	21 (15.6)	25 (18.4)
Right coronary artery	114 (42.1)	59 (43.7)	55 (40.4)
Infarct-related artery TIMI flow – No. (%)			
Preintervention grade			
0	153 (56.5)	72 (53.3)	81 (59.6)
1	21 (7.7)	10 (7.4)	11 (8.1)
2	47 (17.3)	30 (22.2)	17 (12.5)
3	50 (18.5)	23 (17.0)	27 (19.9)
Postintervention grade			
2	17 (6.3)	10 (7.4)	7 (5.1)
3	254 (93.7)	125 (92.6)	129 (94.9)
Myocardial blush grade – No. (%)			
0	5 (1.9)	1 (0.8)	4 (2.9)
1	19 (7.1)	11 (8.3)	8 (5.9)
2	57 (21.2)	28 (21.1)	29 (21.3)
3	188 (69.9)	93 (69.9)	95 (69.9)
<i>Continued</i>			
Characteristic	Total (n=271)	Metformin (n=135)	Control (n=136)
Laboratory values at admission			
CK, median (IQR), U/l	134 (92–215)	143 (93–280)	127 (89–184)

Myocardial band of CK, median (IQR), U/l	17 (13–25)	18 (14–33)	13 (13–23)
Creatinine, median (IQR), $\mu\text{mol/l}$	72 (64–82)	71 (62–85)	73 (64–80)
NT-proBNP, median (IQR), ng/l	80 (38–188)	80 (39–238)	80 (38–178)
Glucose, median (IQR), mmol/l	8.2 (7.2–9.5)	8.5 (6.9–9.6)	8.1 (7.0–9.3)
HbA1c, median (IQR), %	5.8 (5.6–6.0)	5.8 (5.6–6.1)	5.9 (5.7–6.1)
Abbreviations: SD, standard deviation, PCI, percutaneous coronary intervention; IQR, interquartile range; TIMI, Thrombolysis in Myocardial Infarction; CK, creatine kinase; NT-proBNP, N-terminal pro brain natriuretic peptide; HbA1c, glycated hemoglobin.			

eTable 3. Comparison of Baseline Characteristics by Primary End Point Assessment

Characteristic	Total (n=379)	LVEF by MRI (n=271)	No LVEF by MRI (n=108)
Age, mean (SD), years	58.8±11.6	57.7±11.6)	61.5±11.4
Female sex – No. (%)	95 (25.1)	58 (21.4)	37 (34.3)
Body-mass Index, mean (SD), kg/m ²	27.0±3.8	26.9±3.5	27.1±4.6
Race or ethnic group – No. (%)			
Caucasian	365 (96.3)	257 (94.8)	108 (100)
Asian	10 (2.6)	10 (3.7)	0
Black	4 (1.1)	4 (1.5)	0
Cardiovascular related history – No. (%)			
Hypertension	112 (30.0)	75 (27.7)	37(34.3)
Dyslipidemia	239 (63.1)	168 (62.0)	71 (65.7)
Current smoking	209 (55.1)	139 (51.3)	70 (64.8)
Stroke	3 (0.8)	1 (0.4)	2 (1.9)
Peripheral artery disease	0	0	0
Previous PCI	3 (0.8)	4 (1.5)	0
Blood pressure, mean (SD), mmHg			
Systolic	134±23	132±22	138±26
Diastolic	84±15	84±15	84±15
Heart rate, mean (SD), beats/min	76±16	76±16	76±18
Ischemia time, median (IQR), min	161 (109–250)	155 (105–240)	177 (122–262)
Single vessel disease – No. (%)	258 (68.1)	195 (72.0)	63 (58.3)
Infarct-related artery – No. (%)			
Left main	0	0	0
Left anterior descending coronary	146 (38.5)	111 (41.0)	35 (32.4)
Left circumflex coronary artery	64 (16.9)	46 (17.0)	18 (16.7)
Right coronary artery	169 (44.6)	114 (42.1)	55 (50.9)
Infarct-related artery TIMI flow – No. (%)			
Preintervention grade			
0	208 (54.9)	153 (56.5)	55 (50.9)
1	27 (7.1)	21 (7.7)	6 (5.6)
2	66 (17.4)	47 (17.3)	19 (17.6)
3	78 (20.6)	50 (18.5)	28 (25.9)
Postintervention grade			
2	34 (9.0)	17 (6.3)	17 (15.7)
3	345 (91.0)	254 (93.7)	91 (84.3)
Myocardial blush grade – No. (%)			
0	10 (2.6)	5 (1.9)	5 (4.7)
1	29 (7.7)	19 (7.1)	10 (9.3)
2	74 (19.5)	57 (21.2)	17 (15.9)
3	263 (69.4)	188 (69.9)	75 (70.1)
<i>Continued</i>			
Characteristic	Total (n=379)	LVEF by MRI (n=271)	No LVEF by MRI (n=108)
Laboratory values at admission			
CK, median (IQR), U/l	129 (83–210)	134 (92–215)	108 (72–191)
Myocardial band of CK, median (IQR), U/l	16 (13–25)	17 (13–25)	15 (11–23)
Creatinine, median (IQR), μmol/l	72 (62–82)	72 (64–82)	71 (60–81)

NT-proBNP, median (IQR), ng/l	81 (40–200)	80 (38–188)	83 (40–217)
Glucose, median (IQR), mmol/l	8.2 (7.0–9.6)	8.2 (7.2–9.5)	8.3 (7.3–10.3)
HbA1c, median (IQR), %	5.8 (5.6–6.0)	5.8 (5.6–6.0)	5.8 (5.6–6.1)
Abbreviations: SD, standard deviation, PCI, percutaneous coronary intervention; IQR, interquartile range; TIMI, Thrombolysis in Myocardial Infarction; CK, creatine kinase; NT-proBNP, N-terminal pro brain natriuretic peptide; HbA1c, glycated hemoglobin.			

eTable 4. Clinical Outcomes at 4 Months by Primary End Point Assessment

Outcome	No. (%)			P-Value
	Total (n=379)	LVEF by MRI (n=271)	No LVEF by MRI (n=108)	
Death, reinfarction or target lesion revascularization	8 (2.1)	6 (2.2)	2 (1.9)	0.82
Death	0	0	0	
Reinfarction	7 (1.8)	5 (1.8)	2 (1.9)	1.00
ST-segment elevation myocardial infarction	2 (0.5)	1 (0.4)	1 (0.9)	0.50
Non-ST-segment elevation myocardial infarction	5 (1.3)	4 (1.5)	1 (0.9)	0.67
Stent thrombosis	3 (0.8)	2 (0.7)	1 (0.9)	0.85
Ischemia driven reintervention	15 (4.0)	11 (4.1)	4 (3.7)	0.87
Target lesion revascularization	4 (1.1)	3 (1.1)	1 (0.9)	0.87
Target vessel revascularization	3 (0.8)	1 (0.4)	2 (1.9)	0.15
Non-target vessel revascularization	8 (2.1)	7 (2.6)	1 (0.9)	0.32
Coronary artery bypass grafting	1 (0.3)	0	1 (0.9)	0.12
Hospitalization for heart failure	2 (0.5)	1 (0.4)	1 (0.9)	0.50
Hospitalization for chest pain	24 (6.3)	19 (7.0)	5 (4.6)	0.39
Internal cardiac defibrillator implantation	3 (0.8)	2 (0.7)	1 (0.9)	0.85
Stroke	1 (0.3)	0	1 (0.9)	0.11
Diabetes	59 (15.6)	41 (15.4)	18 (21.4)	0.32
Definitions are available in the Online-Only Material (eMethods2).				