Journal of Geriatric Cardiology (2020) 17: 554–560

Research Article · Open Access ·

Effects and mechanisms of glucose-insulin-potassium on post-procedural myocardial injury after percutaneous coronary intervention

Yi-Dan HAO[1,*], Peng HAO[1,*], Zheng WANG[2], Ying-Xin ZHAO[1], Zhi-Ming ZHOU[1], Yu-Yang LIU[1], De-An JIA[1], Hong-Ya HAN[1], Bin HU[1], Hua SHEN[1], Fei GAO[1], Guo-Zhong PAN[3], Zhen-Feng GUO[4], Shi-Wei YANG[1,#], Yu-Jie ZHOU[1,#]

[1]*Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Disease, the Key Laboratory of Remodeling-related Cardiovascular Disease, Ministry of Education, Beijing, China*
[2]*Peking University Third Hospital, Beijing, China*
[3]*Dongzhimen Hospital Eastern Affiliated to Beijing University of Chinese Medicine, Beijing, China*
[4]*Benq Medical Center, Nanjing Medical University, Nanjing, China*

Abstract

Objective To evaluate the effects and mechanisms of glucose-insulin-potassium (GIK) on post-procedural myocardial injury (PMI) after percutaneous coronary intervention (PCI). **Methods** A total of 200 non-diabetic patients with documented coronary heart disease (CHD) were divided into the Group GIK and Group G, with 100 patients in each group. Patients in Group G were given intravenous infusion of glucose solution 2 hours before PCI. As compared, patients in Group GIK were given GIK. **Results** Both post-procedural creatine phosphokinase isoenzyme MB (CK-MB; 62.1 ± 47.8 *vs.* 48.8 ± 52.6 U/L, $P = 0.007$) and cTnI (0.68 ± 0.83 *vs.* 0.19 ± 0.24 ng/mL, $P < 0.001$) in Group GIK were significantly higher than those in Group G. In Group G, 9.0% and 4.0% of patients had post-procedural increases in CK-MB 1-3 times and > 3 times, which were significantly lower than those in Group GIK (14.0% and 7.0%, respectively; all P values < 0.01); 13.0% and 7.0% of patients had post-procedural increases in cTnI 1-3 times and > 3 times, which were also significantly lower than those in Group GIK (21.0% and 13.0%, respectively; all $P < 0.001$). Pre-procedural (10.2 ± 4.5 *vs.* 5.1 ± 6.3, $P < 0.001$) and post-procedural rapid blood glucose (RBG) levels (8.9 ± 3.9 *vs.* 5.3 ± 5.6, $P < 0.001$) in Group G were higher than those in Group GIK. In adjusted logistic models, usage of GIK (compared with glucose solution) remained significantly and independently associated with higher risk of post-procedural increases in both CK-MB and cTnI levels > 3 times. Furthermore, pre-procedural RBG levels < 5.0mmol/L were significantly associated with higher risk of post-procedural increases in both CK-MB and cTnI levels. **Conclusions** In non-diabetic patients with CHD, the administration of GIK may increase the risk of PMI due to hypoglycemia induced by GIK.

J Geriatr Cardiol 2020; 17: 554–560. doi:10.11909/j.issn.1671-5411.2020.09.004

Keywords: Glucose-insulin-potassium; Post-procedural myocardial injury; Percutaneous coronary intervention; Hypoglycemia

1 Introduction

Post-procedural myocardial injury (PMI) is one of the major complications of percutaneous coronary intervention (PCI), defined as creatine phosphokinase isoenzyme MB (CK-MB) and/or cardiac troponin (cTn) elevation above the 99th centile upper reference limit (URL).[1–3] Long-term follow-up studies revealed that elevated CK-MB and cTn significantly increased the risk of adverse cardiovascular events in patients underwent PCI.[1–6] How to reduce PMI is an ongoing topic of concern in the field of cardiovascular research in recent years. In 1962, Sodi-pallares, *et al.*[7] first proposed that the solution of glucose-insulin-potassium (GIK), namely the polarized fluid, could be used to treat myocardial ischemia/reperfusion injury (IRI). Opie, *et al.*[8–13] further explained the probable mechanisms of its cardioprotection and proposed the concept of metabolic therapy. However, with a large number of basic and clinical studies, the efficacy of GIK is still controversial and the exact mechanisms are unclear. GIK has been reported to cause hypoglycemic events.[14–29] We found that mild to

[*]The authors contributed equally to this paper, and are listed alphabetically.

[#]**Correspondence to:** Shi-Wei YANG & Yu-Jie ZHOU, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Disease, the Key Laboratory of Remodeling-related Cardiovascular Disease, Ministry of Education, No. 2 Anzhen Road, Chao Yang District, Beijing 100029, China. E-mails: jackydang@163.com (YANG SW); azzyj_12@163.com (ZHOU YJ)

Received: June 22, 2020 **Revised:** September 25, 2020
Accepted: September 26, 2020 **Published online:** September 28, 2020

moderately decreased fasting plasma glucose levels (≤ 5 mmol/L) might be associated with a relative increase in risk of mortality, especially in patients with acute coronary syndrome (ACS).[30–32] Also, we have reviewed the effects of hypoglycemia on cardiovascular events from the perspective of physiology and pathophysiology.[33] This study aimed to evaluate the effects and mechanisms of GIK compared with the solution of glucose on PMI. We hypothesized that the administration of GIK might increase the risk of PMI due to hypoglycemia induced by GIK.

2 Methods

2.1 Study design and patient population

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Review Boards of each participating institution. Written informed consent was obtained from each patient. A total of 200 patients with documented coronary heart disease (CHD) were selected from September 1, 2018 to December 31, 2019 in three tertiary medical centers. According to the random number table, all patients were divided into the experimental group (Group GIK) and the control group (Group G), with 100 patients in each group. Inclusion criteria were: (1) age at least 18 years; (2) patients with significant coronary artery obstruction in at least one major vessel (stenosis > 50% in left main or > 70% in any other epicardial artery); (3) all patients receiving successful PCI without significant residual stenosis in the target vessel; (4) without history of diabetes and/or hypoglycemic drugs usage; and (5) hemoglobin A1c (HbA1c) < 6.5% and fasting blood glucose < 7.0 mmol/L before PCI. Patients with hemodynamic or cardiac electrical instability, contraindications for PCI, significant comorbidities, or unable to give informed consent were excluded from the study. Note that inclusion in other clinical trials did not preclude enrollment in this study.

Patients in Group G were given intravenous infusion of 500 mL 10% glucose solution 2 h before PCI. As compared, patients in Group GIK were given intravenous infusion of GIK (10% glucose solution 500 mL + 10% potassium chloride 10 mL + insulin 12 U) 2 h before PCI. All procedures were performed by experienced senior physicians who were qualified for PCI. Rapid blood glucose (RBG) levels were measured immediately before and after PCI in all patients. Throughout this article, any reference to plasma myocardial injury biomarkers levels, including CK-MB and cTn, will pertain to that obtained at baseline (after an overnight fast of at least 8 h within 24 h of admission) and 24 h after PCI. During hospitalization, patients were treated with aspirin, clopidogrel, ticagrelor, low molecular weight heparin (LMWH), statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and others according to practice guidelines. As is their routine, center staff abstracted demographic, clinical, and procedural data.

2.2 Statistical analysis

All case record form data were entered into Epidata 3.1 databases (Epidata Association) by different people. Analyses were conducted with SPSS statistical software, version 22.0 (IBM Inc). Continuous variables will be recorded as mean ± SD. Categorical variables will be recorded as counts. The difference between groups will be analyzed using the student *t*-test to compare the mean values of biomarker abnormalities. Categorical variables will be compared between groups using the chi-square test. All statistical tests were two-sided and *P*-values of < 0.05 was considered to be statistically significant.

3 Results

3.1 Baseline demographic and clinical characteristics

Overall, the mean age of the cohort was 60.6 ± 10.8 years old, and 111 (55.5%) patients were males. There were 24 (12.0%), 11 (5.5%), 99 (44.5%) and 37 (18.5%) patients with the history of previous myocardial infarction, stroke, hypertension and hyperlipidemia, respectively. Among all patients, 8.5% were type A lesions, 52.0% type B lesions, and 39.5% type C lesions. As shown in Table 1, there were no significant differences in all baseline demographic and clinical characteristics between groups.

3.2 Comparison of fasting plasma glucose and rapid blood glucose levels between groups

As shown in Table 2, there were no significant differences in baseline fasting plasma glucose (FPG) levels between Group G (5.3 ± 0.6 mmol/L) and Group GIK (5.3 ± 0.5 mmol/L), $P = 0.784$. However, pre-procedural (10.2 ± 4.5 *vs.* 5.1 ± 6.3, $P < 0.001$) and post-procedural RBG levels (8.9 ± 3.9 *vs.* 5.3 ± 5.6, $P < 0.001$) in Group G were much higher than those in Group GIK. Compared with Group G, there were 4 (4.0% *vs.* 0, $P < 0.001$) and 3 (3.0% *vs.* 0, $P < 0.001$) patients in Group GIK with pre- and post-procedural RBG levels < 5.0mmol/L, respectively. Furthermore, in Group GIK the minimum pre- and post-procedural RBG levels were 4.0 and 3.6 mmol/L, respectively.

Table 1. Baseline demographic and clinical characteristics.

Characteristics	Group G (*n* = 100)	Group GIK (*n* = 100)	*P*-value
Age, yrs	61.0 ± 10.3	60.2 ± 10.2	0.306
Male	55 (55.0%)	56 (56.0%)	0.724
Hypertension	48 (48.0%)	51 (51.0%)	0.117
Hyperlipidemia	19 (19.0%)	18 (18.0%)	0.562
Prior myocardial infarction	11 (11.0%)	13 (13.0%)	0.193
Prior stroke	6 (6.0%)	5 (5.0%)	0.891
HbA1c, %	5.5 ± 1.1	5.6 ± 1.4	0.448
Creatinine, μmol/L	70.8 ± 20.3	72.4 ± 19.5	0.146
LDL-C, mmol/L	2.6 ± 0.8	2.6 ± 0.9	0.375
HDL-C, mmol/L	1.0 ± 0.4	1.0 ± 0.3	0.571
K^+, mmol/L	4.3 ± 0.5	4.2 ± 0.6	0.490
LVEF	58.2% ± 11.3%	56.7% ± 10.8%	0.104
Type of lesions in coronary artery disease			
Type-A lesion	9 (9.0%)	8 (8.0%)	
Type-B lesion	51 (51.0%)	53 (53.0%)	0.479
Type-C lesion	40 (40.0%)	39 (39.0%)	
Aspirin	99 (99.0%)	100 (100.0%)	0.863
Clopidogrel	87 (87.0%)	83 (83.0%)	0.592
Ticagrelor	13 (13.0%)	17 (17.0%)	0.086
LMWHs	51 (51.0%)	46 (46.0%)	0.250
Statins	97 (97.0%)	99 (99.0%)	0.926
β-blockers	76 (76.0%)	80 (80.0%)	0.138
ACEIs	49 (49.0%)	46 (46.0%)	0.373
ARBs	30 (30.0%)	28 (28.0%)	0.406

Data are presented as mean ± SD or *n* (%). ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LMWHs: low molecular weight heparin; LVEF: left ventricular ejection fraction.

Table 2. Comparison of fasting plasma glucose and rapid blood glucose levels between groups.

Characteristics	Group G, *n* = 100	Group GIK, *n* = 100	*P*-value
Baseline FPG, mmol/L	5.3 ± 0.6	5.3 ± 0.5	0.784
Pre-procedural RBG, mmol/L	10.2 ± 4.5	5.1 ± 6.3	< 0.001
Post-procedural RBG, mmol/L	8.9 ± 3.9	5.3 ± 5.6	< 0.001
Pre-procedural RBG < 5.0 mmol/L	0	4 (4.0%)	< 0.001
Post-procedural RBG < 5.0 mmol/L	0	3 (3.0%)	< 0.001

Data are presented as mean ± SD or *n* (%). FPG: fasting plasma glucose; GIK: glucose-insulin-potassium; RBG: rapid blood glucose.

3.3 Comparison of myocardial injury biomarkers levels between groups

As shown in Table 3, there were no significant differences in pre-procedural myocardial injury biomarkers levels between Group G and Group GIK (CK-MB: 18.0 ± 11.2 *vs.* 17.9 ± 14.5 U/L, $P = 0.336$; cTnI: 0.01 ± 0.02 *vs.* 0.02 ± 0.02 ng/mL, $P = 0.483$). However, both post-procedural CK-MB (62.1 ± 47.8 *vs.* 48.8 ± 52.6 U/L, $P = 0.007$) and cTnI levels (0.68 ± 0.83 *vs.* 0.19 ± 0.24 ng/mL, $P < 0.001$) in Group GIK were significantly higher than those in Group G.

In Group G, 9.0% and 4.0% of patients had post-procedural increases in CK-MB 1 to 3 times and > 3 times above the URL (25U/L), which were significantly lower than those in Group GIK (14.0% and 7.0%, respectively; all $P < 0.01$); 13.0% and 7.0% of patients had post-procedural increases in cTnI 1 to 3 times and > 3 times above the URL (0.05 ng/mL), which were also significantly lower than those in Group GIK (21.0% and 13.0%, respectively; all *P* values < 0.001).

3.4 Association between usage of GIK or glucose solution with post-procedural increases in myocardial injury biomarkers levels

To evaluate the association between usage of GIK or

Table 3. Comparison of myocardial injury biomarkers levels between groups.

Characteristics	Group G (*n* = 100)	Group GIK (*n* = 100)	*P*-value
Pre-procedural CK-MB, U/L	18.0 ± 11.2	17.9 ± 14.5	0.336
Pre-procedural cTnI, ng/mL	0.01 ± 0.02	0.02 ± 0.02	0.483
Post-procedural CK-MB, U/L	48.8 ± 52.6	62.1 ± 47.8	0.007
Post-procedural cTnI, ng/mL	0.19 ± 0.24	0.68 ± 0.83	< 0.001
Post-procedural increase in CK-MB 1–3 times, %	9 (9.0%)	13 (13.0%)	0.008
Post-procedural increase in CK-MB >3 times, %	4 (4.0%)	7 (7.0%)	0.002
Post-procedural increase in cTnI 1–3 times, %	14 (14.0%)	21 (21.0%)	< 0.001
Post-procedural increase in cTnI >3 times, %	7 (7.0%)	13 (13.0%)	< 0.001

Data are presented as mean ± SD or *n* (%). CK-MB: creatine kinase MB; cTnI: cardiac troponin I.

glucose solution with post-procedural increases in CK-MB and cTnI levels, we performed logistic regression analysis. After adjustment of baseline demographic and clinical characteristics (including age, gender, previous myocardial infarction, stroke, hypertension, fasting plasma glucose, HbA1c, creatinine, LDL-C, HDL-C, LVEF, type of lesions in coronary artery disease, and pharmacological treatment during hospitalization) in logistic models, usage of GIK (compared with glucose solution) remained significantly and independently associated with higher risk of post-procedural increases in both CK-MB and cTnI levels > 3 times above the URL (OR for post-procedural increases in CK-MB >3 times: 1.252, 95% CI: 1.097–1.869, $P = 0.018$; OR for post-procedural increases in cTnI >3 times: 1.443, 95% CI: 1.260–2.794, $P = 0.014$). Furthermore, usage of GIK tended to, but not significantly, be associated with higher risk of post-procedural increases in cTnI levels 1 to 3 times above the URL (OR: 1.175, 95% CI: 0.974–1.901, $P = 0.062$).

3.5 Association between glucose levels with post-procedural increases in myocardial injury biomarkers levels

Whether in unadjusted or adjusted models, baseline FPG level was not significantly associated with post-procedural increases in myocardial injury biomarkers levels. After adjustment of baseline demographic and clinical characteristics (including age, gender, previous myocardial infarction, stroke, hypertension, fasting plasma glucose, HbA1c, creatinine, LDL-C, HDL-C, LVEF, type of lesions in coronary artery disease, and pharmacological treatment during hospitalization), pre-procedural RBG levels < 5.0 mmol/L were significantly associated with higher risk of post-procedural increases in both CK-MB and cTnI levels above the URL (OR for post-procedural increases in CK-MB 1–3 times: 1.548, 95% CI: 1.040–3.553, $P = 0.048$; OR for post-procedural increases in cTnI 1–3 times: 1.705, 95% CI: 1.317–3.042, $P = 0.009$; OR for post-procedural increases in CK-MB > 3 times: 2.150, 95% CI: 1.539–3.728, $P = 0.002$; OR for post-procedural increases in cTnI > 3 times: 2.482, 95% CI: 1.881–4.563, $P < 0.001$).

4 Discussion

PMI, which range from mild to extreme elevation of cardiac biomarkers, can result from the common complications of PCI such as distal embolisation, side-branch occlusion, coronary dissection and disruption of collateral flow, and IRI, etc.[1–3,34–36] The incidence of PMI varies from 5% to 40%, depending on which one biomarker is detected and the time point of sampling.[1–3,34,35] Compared with CK-MB, cTn is the more sensitive biomarkers of PMI. Levels of cTnI and cTnT will reach the peak value at about 24-h after PCI.[37] Although the incidence of adverse cardiovascular events during hospitalization in patients with CK-MB elevation was the same as that in control group, the cardiovascular mortality was significantly increased in patients with elevated CK-MB level at a mean follow-up of four years.[38] Fuchs, *et al*.[39] found that cTnI level > 0.45 ng/mL after PCI and simultaneously elevated CK-MB and cTnI levels were both independent predictors for adverse cardiovascular events during hospitalization. The PMI-related higher risk of adverse cardiovascular events may be affected by the following mechanisms: (1) decreased left ventricular function; (2) ventricular arrhythmias via a small reentrant circuit in the ventricle as a result of scar formation; and (3) elevation in cardiac biomarkers indicating diffuse coronary atherosclerosis.[40, 41]

In 1962, Sodi-pallares, *et al*.[7] first proposed that GIK could be used to treat IRI. Opie, *et al*.[8–13] then further explained the mechanisms of its cardioprotective effects: (1) providing more energy substrate, and promoting the uptake and utilization of glucose by cardiomyocytes with insulin assistance, so as to eventually promote the functional recovery of ischemic myocardium; (2) activating cardiomyocyte Na^+-K^+-ATPase to promote the uptake of K^+, thereby

stabilizing the polarization state of cell membrane and reducing the occurrence of arrhythmia. However, the efficacy of GIK is still controversial and the exact mechanisms are not clear. In this study, we demonstrate for the first time an independent, highly significant, and positive correlation between the usage of GIK (compared with glucose solution) with higher risk of PMI, which may be due to hypoglycemia induced by GIK.

It has been known that intensive glycemic control may increase the risk of hypoglycemia threefold in patients with diabetes, which have been overlooked or dismissed for a long time.[42] As stated by American Diabetes Association (ADA), the barrier of hypoglycemia precludes maintenance of euglycemia over a lifetime of diabetes.[43] Furthermore, non-diabetic individuals can also experience hypoglycemic events due to iatrogenic or non-iatrogenic factors.[44–47] A large number of trials tend to suggest that hypoglycemia may in fact increase cardiovascular risks and mortality in either diabetic or non-diabetic patients with CHD.[48–58] Usually, hypoglycemia is defined as blood glucose level below 3.9 mmol/L (70 mg/dL) according to the ADA.[33] Whereas, blood glucose level below 3.3 mmol/L (60 mg/dL) was also used to define hypoglycemia in some studies.[33] We reported that mild to moderately decreasing FPG levels (≤ 5 mmol/L) were associated with a relative increase in risk of all-cause mortality in diabetic or non-diabetic patients with ACS.[30–32] Multiple mechanisms may be involved in the impact of hypoglycemia on cardiovascular prognosis, including but not limited to hemodynamic changes, electrophysiological effects, prothrombotic, proinflammatory and atherogenic effects.[33]

In the present study, no severe hypoglycemia, which met the general definitions of hypoglycemia as stated above, occurred in either group. However, both pre- and post-procedural RBG levels decreased significantly in patients infused with GIK compared with glucose solution. Furthermore, there were 4.0% and 3.0% patients in Group GIK with pre- and post-procedural RBG levels < 5.0 mmol/L, which were significantly and independently associated with higher risk of post-procedural increases in myocardial injury biomarkers levels. So far, we have proved the original hypothesis that the administration of GIK may increase the risk of PMI due to hypoglycemia induced by GIK. Because of the small size and open-label design of this study, the results may have some bias and other limitations. It is inconclusive and large randomized controlled trials are needed.

In conclusion, in non-diabetic patients with CHD, the administration of GIK may increase the risk of PMI due to hypoglycemia induced by GIK.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments

The report was supported by grants from the Beijing Nova Program (No. Z121107002512053), the Beijing Health System High Level Health Technology Talent Cultivation Plan (No. 2013-3-013), Beijing Outstanding Talent Training Program (No. 20140000021223ZK32), the National Natural Science Foundation of China (No. 81100143), the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. ZYLX 201303), and the National Key Clinical Speciality Construction Project.

Authors' contributions

All authors contributed to the implementation of the research, discussing the results and giving comments on the manuscript. H.Y.D and H.P contributed to the analysis of the results and writing of the manuscript. Y.S.W, Z.Y.J and Z.Y.X contributed to the design, Y.S.W and Z.Y.J reviewed/edited/proved the manuscript.

References

1 Abu SH, Wohlleben D, Vafaie M, *et al*. Coronary angiography-related myocardial injury as detected by high-sensitivity cardiac troponin T assay. *EuroIntervention* 2016; 12: 337–344.

2 Malik SA, Brilakis ES, Pompili V, Chatzizisis YS. Lost and found: coronary stent retrieval and review of literature. *Catheter Cardiovasc Interv* 2018; 92: 50–53.

3 Zeitouni M, Silvain J, Guedeney P, *et al*. Periprocedural myocardial infarction and injury in elective coronary stenting. *Eur Heart J* 2018; 39: 1100–1109.

4 Fihn SD, Blankenship JC, Alexander KP, *et al*. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2014; 130: 1749–1767.

5 Levine GN, Bates ER, Blankenship JC, *et al*. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI Guideline for

Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. *J Am Coll Cardiol* 2016; 67: 1235–1250.
6 Lüscher TF. Optimizing percutaneous coronary interventions: Heart Team, SYNTAX II Score, physiology and imaging guidance, modern stents, and guideline-based medication. *Eur Heart J* 2017; 38: 3109–3113.
7 Sodi-Pallares D, Ma DE, Medrano G, *et al*. [Effect of glucose-insulin-potassium solutions on the electrocardiogram in acute and chronic cornary insufficiency]. *Mal Cardiovasc* 1962; 3: 41–79. [Article in French].
8 Opie LH. Proof that glucose-insulin-potassium provides metabolic protection of ischaemic myocardium. *Lancet* 1999; 353: 768–769.
9 Apstein CS, Opie LH. Glucose-insulin-potassium (GIK) for acute myocardial infarction: a negative study with a positive value. *Cardiovasc Drugs Ther* 1999; 13: 185–189.
10 Opie LH. Glucose and the metabolism of ischaemic myocardium. *Lancet* 1995; 345: 1520–1521.
11 Oldfield GS, Commerford PJ, Opie LH. Effects of preoperative glucose-insulin-potassium on myocardial glycogen levels and on complications of mitral valve replacement. *J Thorac Cardiovasc Surg* 1986; 91: 874–878.
12 Dalby AJ, Bricknell OL, Opie LH. Effect of glucose-insulin-potassium infusions on epicardial ECG changes and on myocardial metabolic changes after coronary artery ligation in dogs. *Cardiovasc Res 1*981; 15: 588–598.
13 Opie LH, Owen P. Effect of glucose-insulin-potassium infusions on arteriovenous differences of glucose of free fatty acids and on tissue metabolic changes in dogs with developing myocardial infarction. *Am J Cardiol* 1976; 38: 310–321.
14 Avogaro A, Bonora E, Consoli A, *et al*. Glucose-lowering therapy and cardiovascular outcomes in patients with type 2 diabetes mellitus and acute coronary syndrome. *Diab Vasc Dis Res* 2019; 16: 399–414.
15 JAW P, van Steen SCJ, Thiel B, *et al*. Peri-operative management of patients with type-2 diabetes mellitus undergoing non-cardiac surgery using liraglutide, glucose-insulin-potassium infusion or intravenous insulin bolus regimens: a randomised controlled trial. *Anaesthesia* 2018; 73: 332–339.
16 EMA S, Shulman R, Singer M. Experience using high-dose glucose-insulin-potassium (GIK) in critically ill patients. *J Crit Care* 2017; 41: 72–77.
17 Polderman JA, Houweling PL, Hollmann MW, *et al*. Study protocol of a randomised controlled trial comparing perioperative intravenous insulin, GIK or GLP-1 treatment in diabetes-PILGRIM trial. *BMC Anesthesiol* 2014; 14: 91.
18 Shirakawa Y. [High-dose insulin therapy]. *Chudoku Kenkyu* 2012; 25: 201–204. [Article in Japanese].
19 Hirsch IB, O'Brien KD. How to best manage glycemia and non-glycemia during the time of acute myocardial infarction. *Diabetes Technol Ther* 2012; 14 (Suppl 1): S22–S32.
20 Lipton JA, Can A, Akoudad S, Simoons ML. The role of insulin therapy and glucose normalisation in patients with acute coronary syndrome. *Neth Heart J* 2011; 19: 79–84.
21 Goyal A, Mehta SR, Díaz R, *et al*. Differential clinical outcomes associated with hypoglycemia and hyperglycemia in acute myocardial infarction. *Circulation* 2009; 120: 2429–2437.
22 Pittas AG, Siegel RD, Lau J. Insulin therapy and in-hospital mortality in critically ill patients: systematic review and meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr* 2006; 30: 164–172.
23 van der Horst IC, Timmer JR, Ottervanger JP, *et al*. Glucose and potassium derangements by glucose-insulin-potassium infusion in acute myocardial infarction. *Neth Heart J* 2006; 14: 89–94.
24 Visser L, Zuurbier CJ, Hoek FJ, *et al*. Glucose, insulin and potassium applied as perioperative hyperinsulinaemic normoglycaemic clamp: effects on inflammatory response during coronary artery surgery. *Br J Anaesth* 2005; 95: 448–457.
25 Gu W, Pagel PS, Warltier DC, Kersten JR. Modifying cardiovascular risk in diabetes mellitus. *Anesthesiology* 2003; 98: 774–779.
26 Bonnier M, Lönnroth P, Gudbjörnsdottir S, *et al*. Validation of a glucose-insulin-potassium infusion algorithm in hospitalized diabetic patients. *J Intern Med* 2003; 253: 189–193.
27 Wistbacka JO, Nuutinen LS, Lepojärvi MV, *et al*. Perioperative glucose-insulin-potassium infusion in elective coronary surgery: minor benefit in connection with blood cardioplegia. *Infusionsther Transfusionsmed* 1994 ; 21: 160–166.
28 Girard C, Quentin P, Bouvier H, *et al*. Glucose and insulin supply before cardiopulmonary bypass in cardiac surgery: a double-blind study. *Ann Thorac Surg* 1992; 54: 259–263.
29 Husband DJ, Thai AC, Alberti KG. Management of diabetes during surgery with glucose-insulin-potassium infusion. *Diabet Med* 1986; 3: 69–74.
30 Yang SW, Zhou YJ, Liu YY, *et al*. Influence of abnormal fasting plasma glucose on left ventricular function in older patients with acute myocardial infarction. *Angiology* 2012; 63: 266–274.
31 Yang SW, Zhou YJ, Nie XM, *et al*. Effect of abnormal fasting plasma glucose level on all-cause mortality in older patients with acute myocardial infarction: results from the Beijing Elderly Acute Myocardial Infarction Study (BEAMIS). *Mayo Clin Proc* 2011; 86: 94–104.
32 Yang SW, Zhou YJ, Hu DY, *et al*. Association between admission hypoglycaemia and in-hospital and 3-year mortality in older patients with acute myocardial infarction. *Heart* 2010; 96: 1444–1450.
33 Yang SW, Park KH, Zhou YJ. The impact of hypoglycemia on the cardiovascular system: physiology and pathophysiology. *Angiology* 2016; 67: 802–809.
34 Cuculi F, Lim CC, Banning AP. Periprocedural myocardial injury during elective percutaneous coronary intervention: is it important and how can it be prevented. *Heart* 2010; 96: 736–740.
35 Deng KW, Shi XB, Zhao YX, *et al*. The effect of exogenous creatine phosphate on myocardial injury after percutaneous coronary intervention. *Angiology* 2015; 66: 163–168.

36 Bertinchant JP, Polge A, Juan JM, *et al*. Evaluation of cardiac troponin I and T levels as markers of myocardial damage in doxorubicin-induced cardiomyopathy rats, and their relationship with echocardiographic and histological findings. *Clin Chim Acta* 2003; 329: 39–51.
37 Bertinchant JP, Ledermann B, Schmutz L, *et al*. [Diagnostic and prognostic significance of CK-MB, troponins, CRP, BNP and/or NT-proBNP in coronary angioplasty. Elevation mechanisms and clinical implications]. *Arch Mal Coeur Vaiss* 2007. 100: 925–933. [Article in French].
38 Kong TQ, Davidson CJ, Meyers SN, *et al*. Prognostic implication of creatine kinase elevation following elective coronary artery interventions. *JAMA* 1997; 277: 461–466.
39 Fuchs S, Kornowski R, Mehran R, *et al*. Prognostic value of cardiac troponin-I levels following catheter-based coronary interventions. *Am J Cardiol* 2000; 85: 1077–1082.
40 Ishibashi Y, Muramatsu T, Nakatani S, *et al*. Incidence and potential mechanism(s) of post-procedural rise of cardiac biomarker in patients with coronary artery narrowing after implantation of an everolimus-eluting bioresorbable vascular Scaffold or Everolimus-eluting metallic stent. *JACC Cardiovasc Interv* 2015; 8: 1053–1063.
41 Goliasch G, Winter MP, Ayoub M, *et al*. A contemporary definition of periprocedural myocardial injury after percutaneous coronary intervention of chronic total occlusions. *JACC Cardiovasc Interv* 2019; 12: 1915–1923.
42 Monami M, Dicembrini I, Kundisova L, *et al*. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. *Diabetes Obes Metab* 2014; 16: 833–840.
43 Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; 28: 1245–1249.
44 Tsujimoto T, Yamamoto-Honda R, Kajio H, *et al*. High risk of abnormal QT prolongation in the early morning in diabetic and non-diabetic patients with severe hypoglycemia. *Ann Med* 2015: 1–7.
45 Lheureux O, Preiser JC. Year in review 2013: Critical Care--metabolism. *Crit Care* 2014; 18: 571.
46 Eckert-Norton M, Kirk S. Non-diabetic hypoglycemia. *J Clin Endocrinol Metab* 2013; 98: 39A–40A.
47 Nirantharakumar K, Marshall T, Hodson J, *et al*. Hypoglycemia in non-diabetic in-patients: clinical or criminal. *PLoS One* 2012; 7: e40384.
48 Gerstein HC, Miller ME, Byington RP, *et al*. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545–2559.
49 Patel A, MacMahon S, Chalmers J, *et al*. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358: 2560–2572.
50 Moritz T, Duckworth W, Abraira C. Veterans Affairs diabetes trial--corrections. *N Engl J Med* 2009; 361: 1024–1025.
51 de Boer IH, Sun W, Cleary PA, *et al*. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* 2011; 365: 2366–2376.
52 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352: 837–853.
53 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: 1577–1589.
54 Bonds DE, Miller ME, Bergenstal RM, *et al*. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010; 340: b4909.
55 Riddle MC, Ambrosius WT, Brillon DJ, *et al*. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010; 33: 983–990.
56 Duckworth W, Abraira C, Moritz T, *et al*. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; 360: 129–139.
57 Gerstein HC, Bosch J, Dagenais GR, *et al*. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012; 367: 319–328.
58 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329: 977–986.