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# Hyperglycemia during acute myocardial infarction in patients who are treated by primary percutaneous coronary intervention: Impact on long-term prognosis<sup>☆</sup>

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## Abstract

**Background:** Transient hyperglycemia is common during acute myocardial infarction in non-diabetic patients and is associated with a worse outcome. There is limited data on the outcome of patients who undergo primary percutaneous coronary intervention and have transient hyperglycemia.

**Methods:** Fasting plasma glucose was measured in 431 consecutive acute myocardial infarction patients who underwent primary percutaneous coronary interventions. Patients were classified into three groups: non-diabetics/non-hyperglycemic (NDNH, glucose < 126 mg/dL;  $n=224$ ); non-diabetics/hyperglycemic (NDH, glucose  $\geq 126$  mg/dL;  $n=119$ ); and diabetics ( $n=88$ ). Data were analyzed according to the different groups and according to exact glucose levels.

**Results:** In-hospital mortality was significantly lower in NDNH (1%) compared to NDH (8%) and diabetic (5%) patients ( $p=0.01$ ). One-year cumulative mortality was highest (10%) in patients with NDH ( $p<0.001$ ). One year target lesion revascularization rates were identical in NDNH and NDH patients (6% vs. 8%) and higher in diabetic patients (19%,  $p=0.001$ ). In a multivariate model, a striking increase in the risk of death (0.6%,  $p=0.05$ ) and target lesion revascularization (2%,  $p<0.0001$ ) was found for every increment of 1 mg/dL in glucose level.

**Conclusions:** Transient hyperglycemia in non-diabetic acute myocardial infarction patients who undergo primary percutaneous coronary interventions is associated with high one-year mortality. One year target lesion revascularization rates were significantly higher in diabetics compared to non-diabetics with normoglycemia or transient hyperglycemia.

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**Keywords:** Hyperglycemia; Primary PCI; Myocardial infarction

## 1. Introduction

Hyperglycemia is commonly observed during acute myocardial infarction. This may represent in some patients, pre-existing, undiagnosed diabetes mellitus or impaired

glucose tolerance. However, most patients do not qualify for the diagnosis of diabetes mellitus after the acute event, and are classified as non-diabetic patients with stress-induced hyperglycemia. Regardless of whether these patients are diagnosed later as diabetics or not, their risk of mortality and morbidity is markedly increased [1].

It is well established that in diabetic patients with stable coronary artery disease, the incidence of restenosis after percutaneous coronary intervention with or without stents is higher than in non-diabetic patients [2–4]. Furthermore, the risk of neointimal hyperplasia and restenosis after coronary stent implantation, in patients with normal fasting glucose

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levels, is increased in the presence of abnormal glucose tolerance [5] or in patients with insulin resistance [6]. However, diabetic patients who undergo stent implantation while on optimal glycemic control, have one-year target vessel revascularization rate similar to that of nondiabetic patients [7].

The aim of this study was to evaluate the relationship between fasting plasma glucose levels during acute myocardial infarction in patients who undergo primary percutaneous coronary interventions and long term outcome, as assessed by mortality rate and need for target lesion revascularization.

## 2. Methods

Since January 1996 we prospectively included in an ongoing registry all consecutive ST-segment elevation acute myocardial infarction patients who underwent primary percutaneous coronary interventions. Blood glucose was measured after overnight fasting in all patients. We analyzed the clinical and angiographic characteristics and outcomes of all patients enrolled between January 1996 and June 2004. Patients underwent interventions via a transfemoral approach according to current guidelines with conventional catheter-based systems. Weight-adjusted heparin dosage was administered at the beginning of the procedure in order to maintain an activated clotting time of 250–300 seconds and was routinely discontinued at the end of the procedure. Patients received aspirin 200–325 mg before the procedure and continued indefinitely afterwards. Patients who underwent stenting were treated concomitantly with clopidogrel 300 mg loading dose and than 75 mg/day or ticlopidine 250 mg  $\times$  2/d for 4 weeks. Drug eluting stents were not used in any of the patients. The decision of using stents, glycoprotein IIb/IIIa inhibitors, or other medications was according to operator's discretion. Intravenous infusions containing glucose were not used. Plasma glucose was enzymatically determined with the glucose oxidase method using an AutoAnalyzer (Hitachi 747, Japan).

## 3. Definitions

ST-segment elevation myocardial infarction was defined as the presence of ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or 2 adjacent limb leads in patients who had symptoms consistent with infarction. We included in the registry patients who presented within 12 h from symptom onset and who were not treated by thrombolytic agents. Diabetes mellitus was considered to be present if patients had a history of diabetes that was controlled by diet, or with oral hypoglycemic agents or insulin, regardless of duration or were discharged from the hospital with a diagnosis of diabetes and/or hypoglycemic agents. Transient hyperglycemia was defined as the presence of fasting plasma glucose  $>126$  mg/dL (7.0 mmol/l; diabetic range glucose level) in non-diabetic patients, during the first day of hospitalization and these patients were classified as

non-diabetics/hyperglycemic (NDH). Non diabetic patients with glucose levels  $<126$  mg/dL were classified as non-diabetics/non-hyperglycemic (NDNH).

Blood samples were routinely obtained from all patients pre-and post-intervention for the assessment of creatine kinase at 3 hours intervals until peak value was reached and values began decreasing back to normal. Re-infarction was defined as either chest discomfort or new electrocardiographic changes that are accompanied by increase in creatine kinase activity of more than 50% of the previous value, if within 48 hours of the index infarction, or more than 3 times the upper normal limit if after 4 hours [8]. Heart failure was defined as Killip 3 or 4. Major adverse cardiac events in-hospital included death, myocardial infarction and heart failure.

Baseline demographics, angiographic features, and in-hospital outcomes were prospectively recorded and entered into a dedicated database. Mortality records were obtained from the hospital and from the national death registry records. The need for repeat angiographic examinations and revascularization was determined according to clinical status. Patients were interviewed by telephone if they had no repeat hospitalization in our institution, and angiographic data was obtained.

## 4. Statistical analysis

Continuous variables are presented as either means  $\pm$  SD or medians (with interquartile ranges); and dichotomous variables as numbers and percentages. The baseline characteristics of the groups were compared by use of analysis of variance for continuous variables and by the Chi-Square statistic for categorical variables. In hospital outcomes were analyzed by stepwise logistic regression. Long-term event-free survival was estimated by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate Cox proportion models were used to calculate odds ratios for the different groups. In addition, these models were applied without separating to groups, but according to the exact glucose level. For survival adjustment the following baseline

Table 1  
Baseline clinical characteristics

	NDNH n=224	NDH n=119	Diabetes n=88	P -value
Age (years)	56 $\pm$ 12	58 $\pm$ 12	61 $\pm$ 11	0.01
Male Gender (%)	194 (86)	98 (82)	61 (69)	0.002
Previous infarction (%)	43 (19)	28 (24)	22 (25)	0.2
Hyperlipidemia (%)	75 (33)	45 (38)	45 (51)	0.03
Smoking (%)	124 (55)	55 (46)	49 (56)	0.4
Hypertension (%)	74 (33)	36 (30)	43 (49)	0.01
Anterior wall infarction (%)	152 (68)	85 (71)	56 (64)	0.6
Cardiogenic shock (%)	7 (3)	8 (7)	11 (13)	$<0.01$
Killip Class	1.2 $\pm$ 0.6	1.6 $\pm$ 0.9	1.7 $\pm$ 1.1	$<0.0001$
Ejection fraction (%)	49 $\pm$ 8	46 $\pm$ 10	47 $\pm$ 10	0.01
Symptom onset to 1 <sup>st</sup> balloon inflation $>4$ hours (%)	44 (50)	52 (44)	91 (41)	0.3

NDNH, non-diabetics/non-hyperglycemic; NDH, non-diabetics/hyperglycemic.

Table 2  
Angiographic characteristics

	NDNH <i>n</i> =224	NDH <i>n</i> =119	Diabetes <i>n</i> =88	P value
LMCA (%)	3 (1)	3 (3)	0 (0)	0.3
3 vessel disease (%)	49 (22)	33 (28)	24 (27)	0.3
Treated vessel				
LAD	149 (77)	80 (78)	55 (70)	0.3
LCx	21 (15)	5 (7)	11 (16)	0.2
RCA	44 (28)	24 (28)	18 (25)	0.9
Baseline TIMI 3 flow (%)	34 (15)	10 (8)	14 (16)	0.1
Final TIMI 3 flow (%)	202 (90)	101 (85)	76 (86)	0.7
Minimal lumen diameter	2.9±0.46	2.9±0.48	2.8±0.53	0.2
Stent use (%)	211 (94)	111 (93)	82 (93)	0.9
Stent diameter	2.95±0.4	3.1±0.4	±0.43	0.03
Stent length	21±8	23±10	22±10	0.4

NDNH, non-diabetics/non-hyperglycemic; NDH, non-diabetics/hyperglycemic. TIMI, Thrombolysis in Myocardial Infarction.

clinical characteristics were included: age, gender, previous infarction, history of hypertension, time from symptom onset to first balloon inflation, infarct location, Killip class on admission, admission heart rate, admission blood pressure, presence of anterior infarction, left ventricular function by echocardiography, creatinine levels, baseline and final thrombolysis in myocardial infarction flow. For target lesion revascularization adjustments the following variables were used: post procedure minimal lumen diameter, lesion location, use of stents, stent diameter and length, gender, smoking, creatinine levels and previous coronary intervention. Variables found to show association in the univariate analysis ( $P<0.20$ ) were used in the multivariate model. Cox proportional-hazards model was used to estimate the simultaneous effects of prognostic factors on survival and revascularization. Data was analyzed with GraphPad Prism (version 4.0; GraphPad Software, Inc) and SAS statistical system. The level selected for statistical significance was set at probability value  $p<0.05$ .

## 5. Results

Between January 1996 and June 2004, a total of 454 consecutive patients underwent coronary angiography during the acute phase of ST-segment elevation myocardial

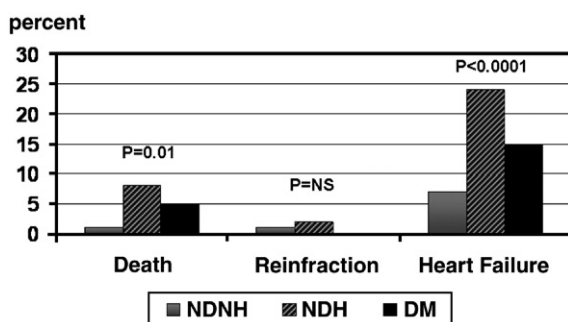


Fig. 1. In-hospital outcomes. DM, diabetes mellitus; NDNH, non-diabetics/non-hyperglycemic; NDH, non-diabetics/hyperglycemic.

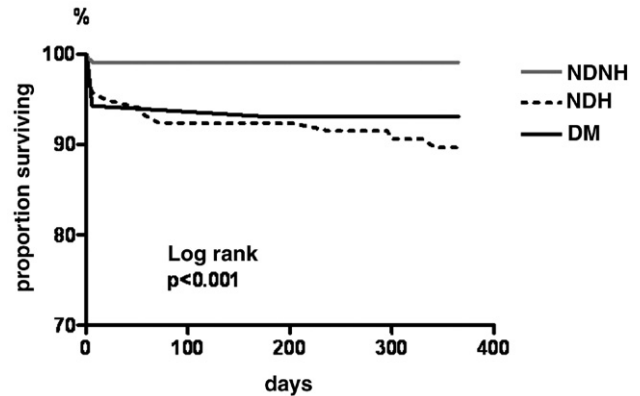


Fig. 2. Kaplan–Meier one-year survival curve. DM, diabetes mellitus; NDNH, non-diabetics/non-hyperglycemic; NDH, non-diabetics/hyperglycemic.

infarction at our institution. Successful intervention was performed in 440 patients. Nine patients died before obtaining fasting plasma glucose. Thus, a total of 431 patients were included in the present analysis. The patients were divided into 3 groups: 1) diabetes mellitus ( $n=88$ , median glucose level of 158 mg/dL (interquartile range, 132 to 209 mg/dL), 2) NDH ( $n=119$ , median glucose level of 150 mg/dL (interquartile range, 136 to 183 mg/dL) and 3) NDNH ( $n=224$ , median glucose level of 99 mg/dL (interquartile range, 91 to 109 mg/dL). Clinical characteristics are shown in Table 1. There were significant differences between the groups in several parameters: diabetic patients were older and more likely to present with cardiogenic shock. In contrast, the NDNH group had higher ejection fraction and better Killip class compared to the other groups. Angiographic characteristics, procedural success and use of stents were similar among the groups (Table 2).

### 5.1. In-hospital outcomes

In hospital outcomes are shown in Fig. 1. In hospital death rates were higher in patients with NDH as compared to

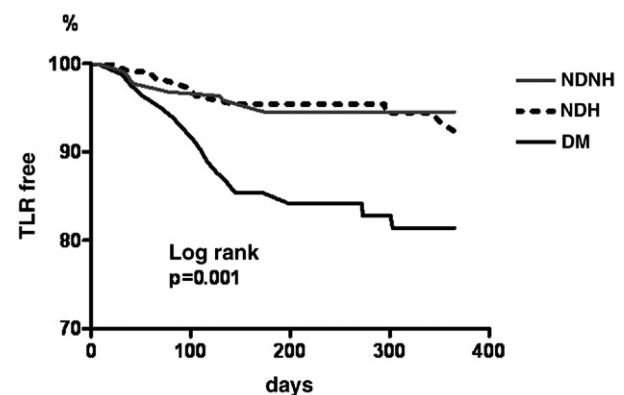


Fig. 3. Kaplan–Meier one-year target lesion revascularization (TLR) free. DM, diabetes mellitus; NDNH, non-diabetics/non-hyperglycemic; NDH, non-diabetics/hyperglycemic.

NDNH patients ( $p=0.002$ ) and non-significantly higher compared to diabetic patients. The incidence of heart failure was significantly higher in patients with NDH compared to NDNH patients ( $p<0.0001$ ) (Fig. 1). After adjustment for predictors of mortality (admission Killip class and final thrombolysis in myocardial infarction flow) there were no significant differences in mortality between groups. However, after adjustments for the above covariates, NDH remained an important predictor of in-hospital heart failure as compared to the NDNH group (OR: 3.2, CI: 1.5–6.7;  $p=0.002$ ), whereas diabetes mellitus was not.

### 5.2. Long-term outcomes

Kaplan–Meier 12-month survival was significantly worse in the diabetic and the NDH patients compared to the NDNH patients (OR: 0.08, CI: 0.03–0.3;  $p<0.0001$ , for NDNH vs. hyperglycemic) (Fig. 2). Among the patients who survived the index hospitalization, none of the NDNH patients died during follow-up, whereas there was additional death in the NDH group. ( $p=0.0002$ ). Target lesion revascularization free survival was identical among the NDNH and the NDH groups and significantly better compared to the diabetic patients (Fig. 3).

Unadjusted Cox proportion analysis showed a prominent increase of 1% in the risk of one-year mortality for each rise of 1 mg/dL in glucose level ( $p<0.0001$ ). In contrast, the presence of diabetes mellitus had no effect on mortality. After adjustment for other important covariates (creatinine levels, age, infarct location, Killip score and final thrombolysis in myocardial infarction flow), fasting plasma glucose levels remained an independent predictor of one-year mortality (0.6% incremental risk for every 1 mg/dL increase in glucose level;  $p=0.05$ ). No difference in mortality rate was found in the multivariate model when analysis was according to the three aforementioned groups.

Univariate cox proportion hazard model for target lesion revascularization, disclosed a significant effect of both diabetes mellitus and glucose levels, as well as a significant difference between the study groups. However, in the multivariate model, glucose level remained an independent predictor of target lesion revascularization whereas diabetes mellitus was not (Table 3).

Table 3

Unadjusted and adjusted hazard ratios for target lesion revascularization at one year follow up

	Unadjusted HR	P value	Adjusted HR	P value
Diabetes vs non-diabetes	3.3	<0.001	2.1	0.2
Diabetes vs. NDNH	3.5	0.001	5.6	0.01
NDH vs. diabetes	0.3	0.01	0.4	0.2
NDH vs. NDNH	1.1	0.73	2.1	0.3
Glucose level	1.01	<0.0001	1.02	<0.0001

Hazard ratio (HR) for glucose is for one unit increase. NDNH, non-diabetics/non-hyperglycemic; NDH, non-diabetics/hyperglycemic.

## 6. Discussion

In our registry of patients undergoing primary percutaneous coronary intervention, fasting hyperglycemia was observed in almost half of all patients (44%) and in 35% of non-diabetic patients. NDH patients were more likely to present with cardiogenic shock and have a reduced left ventricular function compared to the NDNH patients. Fasting glucose level in these patients was a predictor of both short and long-term mortality. The need for target lesion revascularization at one year follow-up was similar to that of NDNH patients and well below that of the diabetic patients. However, the exact glucose level was found to be more important than the presence of diabetes, as a predictor of both death and target lesion revascularization.

Fasting glucose levels of >126 mg/dL (7.0 mmol/l) were chosen to classify the NDH group because this level is used for diagnosis of diabetes mellitus according to the criteria of the American Diabetes Association and the 1999 report of the World Health Organization [9]. It should be mentioned that the definition of impaired fasting glucose is currently 100–125 mg/dL (5.6–6.9 mmol/l) [10] and a graded relation between elevated fasting glucose at levels below 126 mg/dL (7.0 mmol/l) and short-term mortality was reported [11]. However, there is no accepted definition for transient hyperglycemia and therefore we also performed analysis using glucose as a continuous variable. The long-term events were studied during one-year, because after that period non-target lesion events dominate [12].

It is well established that patients who are critically ill release several stress cytokines and steroids and may present with hyperglycemia. There is also a clear association between hyperglycemia and short-term outcome in these patients [13]. In a large study evaluating long-term prognosis after acute MI, non-diabetic patients who had admission blood glucose levels of 200 mg/dL (11.1 mmol/L) or more, had mortality rate similar to that of patients who had established diabetes (42.6% and 43.1% respectively) [14]. Furthermore, elevated admission glucose levels in non-diabetic patients who are treated by reperfusion therapy are independently associated with larger infarct size and poor long-term outcome [15]. Fasting plasma glucose concentrations are even better predictors of short-term mortality than admission levels in non-diabetic patients with acute MI [11]. Whether hyperglycemia is just a marker or plays a pathogenic role in outcome is unknown. Nevertheless, there is data that support the idea that hyperglycemia may be partially responsible for the worse outcome [13].

## 7. Pathophysiological impact of hyperglycemia during acute myocardial infarction

There are several potential explanations for the poor outcome of patients with acute myocardial infarction and acute hyperglycemia: impaired left ventricular function [16], increase of QT interval and QT dispersion possibly leading

to fatal arrhythmias [17], impaired microvascular function with no-reflow phenomenon [18] and the decrease activity of K-ATP channels [19]. Hyperglycemia has a pathogenic role in thrombosis, thrombophilia and platelet aggregation [20]. There is a large body of evidence suggesting association between myocardial infarction and inflammation. The inflammatory process was suggested to be the link between acute hyperglycemia to poor cardiac outcome during myocardial infarction [21]. Other potential explanations linking hyperglycemia and poor outcome after acute myocardial infarction, are reduction of nitric oxide availability and endothelial dysfunction and oxidative stress related to hyperglycemia [22].

Another possible mechanism which could link hyperglycemia with adverse outcome in patients with acute myocardial infarction is a shift from glucose metabolism toward fatty acid metabolism which is more energy demanding [23] and antagonizing the myocardial uptake of glucose, lactate and pyruvate [24]. On the other hand, elevated levels of free fatty acids have been associated with impaired ventricular function in animal models [25] and increased risk of arrhythmias, post-infarct angina, infarct extension, heart failure and death in patients with MI [26].

It was recently shown in analysis of the ON-TIME trial that patients with hyperglycemia are less likely to have thrombolysis in myocardial infarction flow grade 3 before primary percutaneous coronary intervention compared with patients without hyperglycemia [27]. In our study, we observed a non significant decrease in baseline thrombolysis in myocardial infarction flow in hyperglycemic patients and the baseline flow was not a predictor of mortality.

During the early hours of acute myocardial infarction there is increased secretion of catecholamines and glucose intolerance. These abnormalities adversely affect outcome [28]. It is speculated that patients with higher glucose levels have significant glucose intolerance and thus adverse outcome. Facilitation of anaerobic glycolysis could theoretically promote metabolic protection of ischemic myocardium. This issue was investigated in several studies; some of them showed that metabolic modulation using glucose-insulin-potassium infusion is beneficial in patients with acute myocardial infarction. However, this treatment was not effective in the large CREATE-ECLA trial [29]. The effect of glucose-insulin-potassium infusion was also investigated specifically in patients undergoing primary percutaneous coronary intervention. Adjunction of glucose-insulin-potassium infusion resulted in improved ST elevation resolution without effect on long-term outcome [30]. It should be mentioned that normoglycemic patients were also included in these studies but normal glucose levels were not obtained with the glucose-insulin-potassium infusion. It may be speculated that tight glucose control in hyperglycemic patients will lead to different results.

There is limited data concerning the effect of tight glucose control during percutaneous coronary interventions on subsequent need for revascularization. In a study of 239

diabetic patients undergoing elective coronary intervention, optimal glycemic control, defined by HbA1c  $\leq 7\%$ , was associated with target vessel revascularization rates similar to that of non-diabetic patients [7]. In non-diabetic patients with normal fasting plasma glucose who underwent elective coronary interventions, patients who had abnormal glucose tolerance had smaller minimal lumen diameter with a greater degree of restenosis and late loss at 6-month follow-up compared with patients who had normal glucose tolerance [5]. In our study, the group of non-diabetic hyperglycemic patients had clinical restenosis rates similar to that of NDNH patients. However, glucose levels were found to be an independent predictor of clinical restenosis whereas diabetes was not. Potential explanation is that patients with hyperglycemia during myocardial infarction, both diabetics and non-diabetics, have an uncontrolled metabolic state.

### 7.1. Limitations

In our registry the decision to perform follow-up angiography was made by the treating physician if symptoms or non-invasive test results were suggestive of ischemia. Accordingly, clinically silent restenosis cannot be evaluated.

Patients were divided to diabetes mellitus and non-diabetes mellitus groups mainly according to previous diagnosis of diabetes mellitus. Diagnosis of diabetes according to glucose measurements during myocardial infarction is unreliable [31]. It is estimated that 4% of patients admitted with acute myocardial infarction are newly diagnosed with diabetes following the index infarction [32]. It is possible that some of our “non-diabetic” patients had undiagnosed diabetes. Nevertheless, the important predictor of both death and target lesion revascularization was glucose level and not diabetes. Furthermore, target lesion revascularization rates in the non-diabetic patients with hyperglycemia were lower than in diabetic patients and comparable to those of NDNH patients.

### 7.2. Conclusions

In patients with acute myocardial infarction treated by primary percutaneous coronary intervention, fasting hyperglycemia is associated with significant long-term mortality. Whether an attempt to achieve normoglycemia is beneficial in these patients has to be elucidated.

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### References

- [1] Ceriello A. Acute hyperglycaemia: a ‘new’ risk factor during myocardial infarction. *Eur Heart J* 2004;26(4):328–31.

- [2] Aronson D, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. *J Am Coll Cardiol* 1996;27(3):528–35.
- [3] Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1996;94(8):1818–25.
- [4] Mathew V, Gersh BJ, Williams BA, et al. Outcomes in patients with diabetes mellitus undergoing percutaneous coronary intervention in the current era: a report from the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. *Circulation* 2004;109(4):476–80.
- [5] Nakamura N, Ueno Y, Tsuchiyama Y, Koike Y, Gohda M, Satani O. Isolated post-challenge hyperglycemia in patients with normal fasting glucose concentration exaggerates neointimal hyperplasia after coronary stent implantation. *Circ J* 2003;67(1):61–7.
- [6] Piatti P, Di Mario C, Monti LD, et al. Association of insulin resistance, hyperleptinemia, and impaired nitric oxide release with in-stent restenosis in patients undergoing coronary stenting. *Circulation* 2003;108(17):2074–81.
- [7] Corpus RA, George PB, House JA, et al. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. *J Am Coll Cardiol* 2004;43(1):8–14.
- [8] Hofma SH, Ong ATL, Aoki J, et al. One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005;91(9):1176–80.
- [9] Definition, Diagnosis, and Classification of Diabetes Mellitus and Its Complications, Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, Switzerland: World Health Organization; 1999.
- [10] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up Report on the Diagnosis of Diabetes Mellitus. *Diabetes Care* 2003;26(11):3160–7.
- [11] Suleiman M, Hammerman H, Boulous M, et al. Fasting Glucose Is an Important Independent Risk Factor for 30-Day Mortality in Patients With Acute Myocardial Infarction: A Prospective Study. *Circulation* 2005;111(6):754–60.
- [12] Cutlip DE, Chhabra AG, Baim DS, et al. Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. *Circulation* 2004;110(10):1226–30.
- [13] Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2004;164(18):2005–11.
- [14] Stranders I, Diamant M, van Gelder RE, et al. Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. *Arch Intern Med* 2004;164(9):982–8.
- [15] Timmer JR, van dH I, Ottervanger JP, et al. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. *Am Heart J* 2004;148(3):399–404.
- [16] Ishihara M, Inoue I, Kawagoe T, et al. Impact of acute hyperglycemia on left ventricular function after reperfusion therapy in patients with a first anterior wall acute myocardial infarction. *Am Heart J* 2003;146(4):674–8.
- [17] Marfella R, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D. The effect of acute hyperglycaemia on QTc duration in healthy man. *Diabetologia* 2000;43(5):571–5.
- [18] Iwakura K, Ito H, Ikushima M, et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. *J Am Coll Cardiol* 2003;41(1):1–7.
- [19] LaDisa Jr JF, Krolikowski JG, Pagel PS, Wartier DC, Kersten JR. Cardioprotection by glucose–insulin–potassium: dependence on KATP channel opening and blood glucose concentration before ischemia. *Am J Physiol Heart Circ Physiol* 2004;287(2):H601–7.
- [20] Shechter M, Merz CN, Paul-Labrador MJ, Kaul S. Blood glucose and platelet-dependent thrombosis in patients with coronary artery disease. *J Am Coll Cardiol* 2000;35(2):300–7.
- [21] Marfella R, Siniscalchi M, Esposito K, et al. Effects of stress hyperglycemia on acute myocardial infarction: role of inflammatory immune process in functional cardiac outcome. *Diabetes Care* 2003;26(11):3129–35.
- [22] Ceriello A. Acute hyperglycaemia and oxidative stress generation. *Diabet Med* 1997;14(Suppl 3):S45–9.
- [23] Stanley WC, Chandler MP. Energy metabolism in the normal and failing heart: potential for therapeutic interventions. *Heart Fail Rev* 2002;7(2):115–30.
- [24] Vyska K, Meyer W, Stremmel W, et al. Fatty acid uptake in normal human myocardium. *Circ Res* 1991;69(3):857–70.
- [25] Liedtke AJ, Nellis S, Neely JR. Effects of excess free fatty acids on mechanical and metabolic function in normal and ischemic myocardium in swine. *Circ Res* 1978;43(4):652–61.
- [26] Oliver MF, Kurien VA, Greenwood TW. Relation between serum-free-fatty acids and arrhythmias and death after acute myocardial infarction. *Lancet* 1968;1(7545):710–4.
- [27] Timmer JR, Ottervanger JP, de Boer MJ, et al. Hyperglycemia is an important predictor of impaired coronary flow before reperfusion therapy in ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2005;45(7):999–1002.
- [28] Diaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group. *Circulation* 1998;98(21):2227–34.
- [29] Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose–insulin–potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA* 2005;293(4):437–46.
- [30] van dH I, De LG, Ottervanger JP, et al. ST-segment elevation resolution and outcome in patients treated with primary angioplasty and glucose–insulin–potassium infusion. *Am Heart J* 2005;149(6):1135.
- [31] Tenerz A, Lonnberg I, Berne C, Nilsson G, Leppert J. Myocardial infarction and prevalence of diabetes mellitus. Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes? *Eur Heart J* 2001;22(13):1102–10.
- [32] Aguilar D, Solomon SD, Kober L, et al. Newly Diagnosed and Previously Known Diabetes Mellitus and 1-Year Outcomes of Acute Myocardial Infarction: The Valsartan in Acute Myocardial Infarction (VALIANT) Trial. *Circulation* 2004;110(12):1572–8.