European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2013; 17: 1252-1257

Influence of admission glucose profile and hemoglobin A1c on complications of acute myocardial infarction in diabetic patients

S. VUJOSEVIC, N. RADOJEVIC, N. BELADA

Clinical Centre of Montenegro, School of Medicine, University of Montenegro, Podgorica, Montenegro

Abstract. – BACKGROUND: Diabetic patients have a double higher short-term mortality rate after acute myocardial infarction (AMI) than non-diabetic ones. Admission glucose level has been already concerned as an independent risk factor for the long-term prognosis after myocardial infarction. The aim of this study is to evaluate the influence of admission glucose profile (AGP) and glycosylated hemoglobin (HbA1c) on complications of the AMI in patients with type 2 diabetes.

PATIENTS AND METHODS: The study was based on 76 diabetic patients hospitalized with first-ever AMI. Admission glucose profile was estimated as mean value of the first six blood glucose values, since HbA1c was measured from the blood sampled in the first morning after the admission to hospital. All post-infarction complications are divided into electrical and mechanical ones. ROC curves are used to analyze predictive values of admission glucose profile and HbA1c for developing post-infarction complications.

RESULTS: Admission glucose profile is a significant (*p* = 0.001) predictor of electrical complications with 12.25 mmol/L cut-off value (sensitivity 77.3%; specificity 64.5%), while it is not significant (*p* > 0.05) for mechanical complication (cut-off value 16.85 mmol/L; sensitivity 45.2%; specificity 77.8%). HbA1c is not enough good for the complication prediction (*p* > 0.05). Considering electrical and mechanical complications aggregately, AGP is even more significant (*p* = 0.000) with 14.85 mmol/L cut-off value (sensitivity 54.4%; specificity 94.7%), and HbA1c is significant, as well (*p* = 0.013, too with 9.07 % cut-off value (sensitivity 57.9%; specificity 78.8%).

CONCLUSIONS: Comparing the predictability between AGP and HbA1c, in our sample, the first one seems to be the better one. Admission glucose profile and HbA1c should be the obligatory laboratory tests performed at the time of hospital admission after the heart attack.

Key Words:

Admission blood glucose profile, Complications, Type 2 diabetes mellitus, Hemoglobin A1c, Myocardial infarction, Ventricular fibrillation.

Introduction

Cardiovascular diseases are the cause of death in up to 80% patients with type 2 diabetes mellitus (DM)[1]. Absolute risk of death related to the coronary heart disease (CHD) is more than three times higher among diabetic patients than among non diabetic ones[2-4]. A well known fact is that patients with DM have circa the double higher short-term mortality rate after acute myocardial infarction (AMI) than patients without DM[5-7]. A more severe CHD[8,9] with congestive heart failure[10] or cardiomyopathy increased the risk of early reinfarction[11], and more frequent AMI complications[6,7] seem to be the main factors that influence on the lower survival rate in diabetic versus non-diabetic patients. Autonomic neuropathy in DM related to the electrical complication of AIM may contribute to the increased tendency for development of supra and ventricular arrhythmias[2,12]. Post-AMI mechanical complications are related mostly to developing of heart failure, and may be presented as left ventricular remodeling with higher left ventricular filling pressure, left ventricular diastolic dysfunction, or decreased left ventricular ejection fraction[13-16].

Admission glucose level has been already concerned as an independent poor risk factor for long-term prognosis after myocardial infarction[17-19]. Higher admission glucose level (> 180 mg/dL; 9.94 mmol/L) in patients with AMI regardless of DM status is related to higher prevalence of life-threatening arrhythmias and mortality rate, since the admission euglycemic patients (< 120 mg/dL; 6.63 mmol/L) have the lowest prevalence of ventricular tachyarrhythmia[20].

The aim of this study is to evaluate the influence of the admission glucose profile (AGP) and gycosylated hemoglobin (HbA1c) on both electrical (EC) and mechanical complications (MC) of AMI in patients with DM.

Corresponding Author: Nemanja Radojevic, MD; e-mail: com_nr@yahoo.com

Patients and Methods

The study was performed on 76 patients who suffered from type 2 DM hospitalized with a first-ever AMI. The diagnosis of DM was based on the medical records or diabetes diagnosed during the event. The diagnosis of the heart attack was based on patient's subjective symptoms related to the pain, ECG changes typical for AMI, and the level of troponin I (higher that 0.033 µg/L).

AGP was estimated as mean value of the first six separate blood glucose levels, obtained before each of the three daily meals and two hours after them. HbA1c was measured from the blood sampled in the first morning after the hospital admission.

All post AMI complications were divided into *electrical* ones (ventricular tachycardia, ventricular fibrillation, ventricular extrasystolae, atrial fibrillation, and conduction system disorders: the second and the third atrioventricular block), and *mechanical* ones, which are as follows:

- Left ventricular remodeling with higher left ventricular filling pressure, or dilatation of left atrium (reference range 1.9-4 cm), or dilatation and/or hypertrophy of left chamber (reference end-diastolic range 3.5-5.7 cm; reference end-systolic range 2.5-4.1 cm; reference range of posterior wall thickness 0.6-1 cm);
- Left ventricular diastolic dysfunction (estimation of diastolic function by diastolic transmission flow in apical position, and size of E and A waves (if E/A < 1 the diastolic dysfunction exists);
- Regional movement disorders (reference range of wall moving's amplitude is 0.9-1.4 cm);
- Decreased left ventricular systolic ejection fraction (if it is less than 40%).

Only AMI complications developed during the initial hospitalization (early complications) were taken into consideration. EC were diagnosed by standard six-channel ECG, since the ultrasonography (performed by color-Doppler Aloka SSD-870, Tokyo, Japan) was used in determination of the MC.

Statistical Analysis

The statistical evaluation of results was performed by the SPSS ver. 12 for Win software package (SPSS Inc., Chicago, IL, USA). The Receiver Operating Characteristic (ROC) curve was used to assess the levels of AGP and HbA1c predictive for the post AMI complication development. p value below 0.05 was considered as significant, since below 0.01 was highly significant. The ROC curve provides an opportunity to find the cut-off score with the optimal ratio between sensitivity and specificity (or to maximize proportions between true positive ones and true negative ones). Y axis represents sensitivity with values from 0.0 to 1.0 (since the proportions are considered). X axis represents one minus specificity or proportion of false positive ones. If using normalized units, the area under the curve (AUC) is equal to the probability that a classifier will rank a randomly chosen positive case higher than a randomly chosen negative one; e.g. AUC is accuracy of the test.

Student's *t*-test and measures of descriptive statistics were also used.

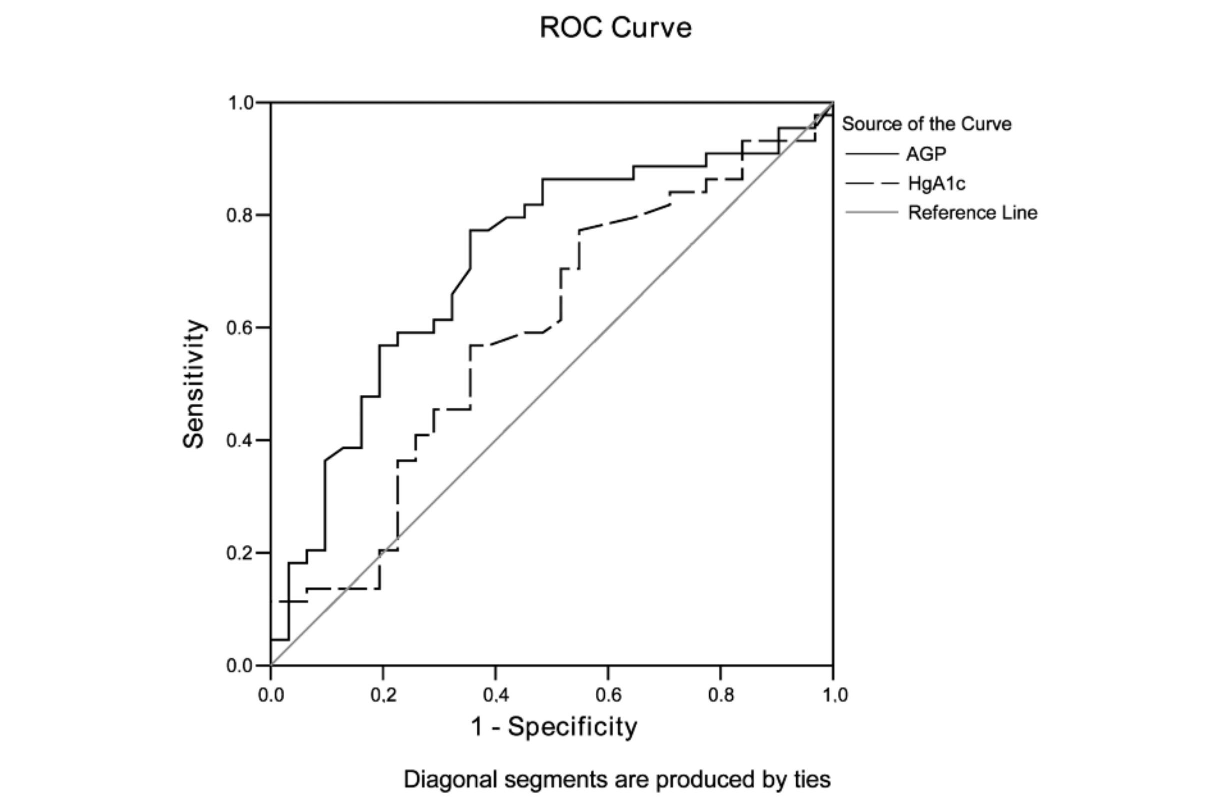
Results

Statistical analysis was performed on 76 patients, mean age 63.41 ± 8.33, min 46, max 81; out of which 36 were females and 40 were males. There is no statistical difference in the age related to the gender (*t*-test, $p > 0.05$).

ROC curves for AGP and HbA1c related to ECs are shown in Figure 1 and in Table I. AUCs with standard errors (SE) and p values with confidence intervals can be found below the chart.. Namely, the accuracy of AGP's predictions of ECs is significantly different from 50:50 chance for the case ($p = 0.001$), since the accuracy that HbA1c does the same is not significantly different ($p > 0.05$). For the match AGP-EC, cut-off value is 12.25 mmol/L (sensitivity 77,3%; specificity 64.5%), since for the match HbA1c-EC cut-off value is 7.05 % (sensitivity 77,3%; specificity 45.2%).

Figure 2 and Table II shows ROC curves for AGP and HbA1c related to MC. None of the matches are significant. The cut-off values for the match AGP-MC, and for the match HbA1c-MC are: 16.85 mmol/L (sensitivity 45.2%; specificity 77.8%), and 12.9 % (sensitivity 29,0%; specificity 91.1%), consequently.

Considering electrical and mechanical complications aggregately (E&MC), ROC curves are presented in Figure 3 and in Table III, in which the match AGP-E&MC is even more significant (p = 0.000) with 14.85 mmol/L cut-off value (sensitivity 54,4%; specificity 94.7%), since the



				95% confidence intervals	
Variable	*AUC*	*SE*	*p*	*Lower limit*	*Upper limit*
AGP	0.718	0.061	0.001	0.599	0.838
HbA1c	0.592	0.068	0.175	0.460	0.725

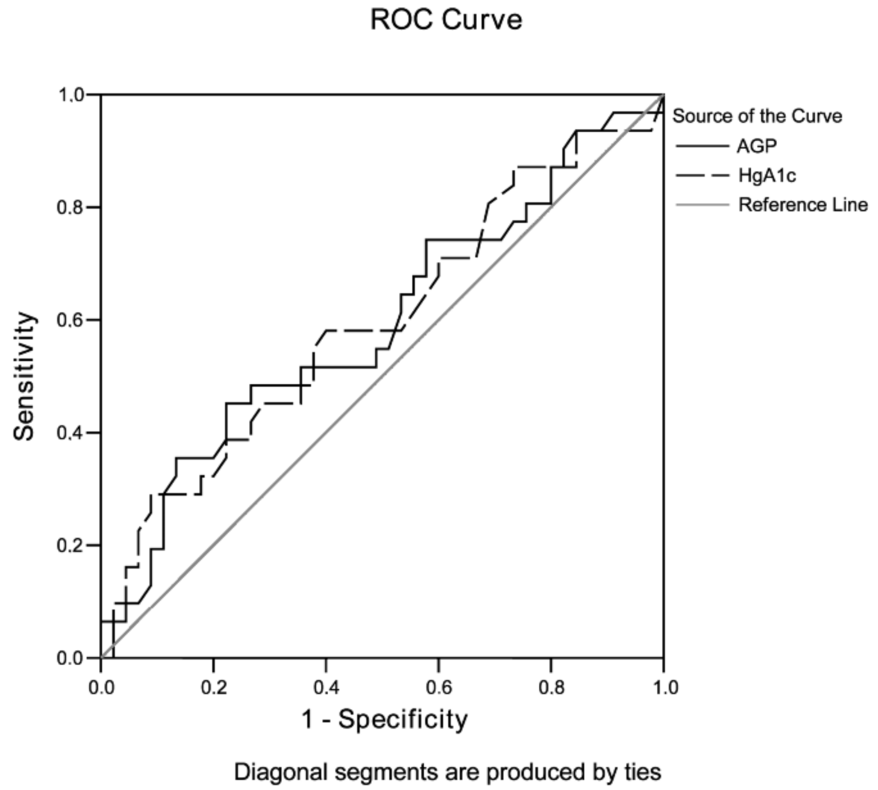
Figure and Table I. ROC curves for AGP and HbA1c related to ECs.

match HbA1c-E&MC is also highly significant ($p = 0.013$), with 9.07 % cut-off value (sensitivity 57,9%; specificity 78.8%).

Discussion

The Framingham study's outcomes[8], revealed that diabetes was associated with a fourfold increase in the risk of chronic heart failure (CHF), even after adjustment for other cardiovascular risk factors (blood pressure, cholesterol level, obesity, etc.). Diabetic patients experience higher rates of CHF following AMI, than non-diabetic ones[10]. Diabetic women in middle age lose their relative protection against CHD compared with men[8], which was confirmed by our study, too, but the reason remains unclear.

Findings of our work are related to the glucose profile at the admission, not a single blood glucose value, as recent publications showed[17-20]. Several prospective studies have confirmed that post-prandial hyperglycemia (after 1h glucose > 11.1 mmol/L) increases a relative risk for morbidity and mortality of cardiovascular diseases[21-23]. From this aspect, AGP was expected to be a better predictor of AMI, since it engages three values of post-load glycemia. Statistical analysis showed that higher values of AGP correlate with a higher appearance of complications of AMI. Values above 12.25 mmol/l are predictive for electrical complications, since values above 14.85 mmol/l are highly predictive for complications, regardless of type. In general, MC considered separately from EC should not be predicted by AGP nor by HbA1c.



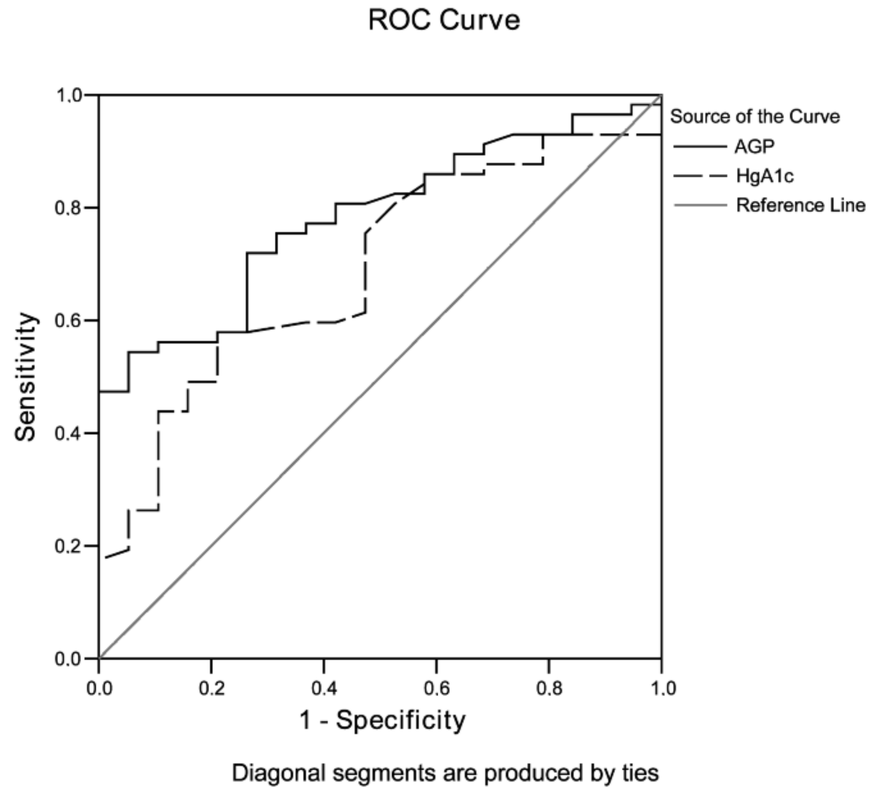
Variable	AUC	SE	*p*	95% confidence intervals	
				Lower limit	Upper limit
AGP	0.593	0.068	0.171	0.460	0.726
HbA1c	0.596	0.068	0.155	0.464	0.729

Figure and Table II. ROC curves for AGP and HbA1c related to MCs.

A well-known fact is that the relative risk for the development of long-term DM complications (retinopathy, nephropathy, and neuropathy) is progressively dependent to the HbA1c increase[24]). Since it is a useful measure for the therapeutic treatment of DM, its value advocates an integrated summary of blood glucose levels during preceding 6-8 weeks[25], but recent investigations exceeded that period to 12 weeks. The European Society of Cardiology's Guidelines for Diabetes[23,26] suggests that for each 1% increase of HbA1c, there is a defined increased risk for cardiovascular disease (14%). In that sense, HbA1c was expected to be a better predictor of post-AMI complications than AGP, but in our sample that hypothesis was not proved. Despite the fact that statistical significance was not achieved when matching HbA1c with EC, nor HbA1c with MC separately, it was achieved while complications had been summarized. Values of HbA1c above 9% sampled in the first morning after admission to the hospital are highly predictive for both types of complications.

Conclusions

AGP is a good predictor for AMI complications, significantly better for the electrical ones, than for the mechanical ones. The AGP measurement should be performed in each case of AMI as the obligatory laboratory test at the time of hospital admission. AGP above 12.25 mmol/L is favorable value related to a higher risk of electrical complications, since values above 14.85 mmol/L and admission values of HbA1c above 9



				95% confidence intervals	
Variable	AUC	SE	p	Lower limit	Upper limit
AGP	0.782	0.053	0.000	0.678	0.886
HbA1c	0.691	0.066	0.013	0.562	0.820

Figure and Table III. ROC curves for AGP and HbA1c related to E&MCs.

% are predictive for both types of complications. Comparing the predictability potential between AGP and HbA1c, in the sample under review here, the AGP seems to be the better one.

Acknowledgements

Authors wish to thank Miroslava Zamaklar MD PhD, for providing the professional assistance.

Conflict of Interest

None declared.

References

1) Buse JB, Polonsky KS, Burant CF. Type 2 diabetes mellitus. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR. Williams Textbook of Endocrinology. 11th Ed. Philadelphia: Saunders Elsevier; 2008. pp. 1329-1388.
2) Brownlee M, Aiello LP, Coopers ME, Vinik AI, Nesto RW, Boulton AJM. Complications of diabetes mellitus: In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR. Williams Textbook of Endocrinology. 11th Ed. Philadelphia: Saunders Elsevier; 2008. pp. 1417-1501.
3) Stamler J, Neaton JD. The Multiple Risk Factor Intervention Trial (MRFIT)--importance then and now. JAMA 2008; 300: 1343-1345.
4) Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation 2000; 102: 1014-1019.
5) Chun BY, Dobson AJ, Heller RF. The impact of diabetes on survival among patients with first myocardial infarction. Diabetes Care 1997; 20: 704-708.
6) Miettinen H, Lehto S, Salomaa V, Mähönen M, Niemelä M, Haffner SM, Pyörälä K, Tuomilehto J.

Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA myocardial infarc¬tion register study group. Diabetes Care 1998; 21: 69-75.

7) Franklin K, Goldberg RJ, Spencer F, Klein W, Budaj A, Brieger D, Marre M, Steg PG, Gowda N, Gore JM; GRACE Investigators. Implications of diabetes in patients with acute coronary syndromes. The Gobal Regis¬try of Acute Coronary Events. Arch Intern Med 2004; 164: 1457-1463.

8) Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974; 34: 29-34.

9) Woodfield SL, Lundergan CF, Reiner JS, Greenhouse SW, Thompson MA, Rohrbeck SC, Deychak Y, Simoons ML, Califf RM, Topol EJ, Ross AM. Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience. J Am Coll Cardiol 1996; 28: 1661-1669.

10) Jacoby RM, Nesto RW. Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course and prognosis. J Am Coll Cardiol 1992; 20: 736-744.

11) Sobel BE, Woodcock-Mitchell J, Schneider DJ, Holt RE, Marutsuka K, Gold H. Increased plasminogen activator inhibitor type 1 in coronary artery atherectomy specimens from type 2 diabetic compared with nondiabetic patients: a potential factor predisposing to thrombosis and its persistence. Circulation 1998; 97: 2213-2221.

12) Zola BE, Vinik AI. Effects of autonomic neuropathy associated with diabetes mellitus on cardiovascular function. Coron Artery Dis 1992; 3: 33-41.

13) Lamblin N, Fertin M, de Groote P, Bauters C. Cardiac remodeling and heart failure after a first anterior myocardial infarction in patients with diabetes mellitus. J Cardiovasc Med (Hagerstown) 2012; 13: 353-359.

14) von Bibra H, St John Sutton M. Impact of diabetes on postinfarction heart failure and left ventricular remodeling. Curr Heart Fail Rep 2011; 8: 242-251.

15) Ren L, Fang X, Wang Y, Qi G. T-wave alternans and heart rate variability: a comparison in patients with myocardial infarction with or without diabetes mellitus. Ann Noninvasive Electrocardiol 2011; 16: 232-238.

16) Andersson C, Gislason GH, Mérie C, Mogensen UM, Solomon SD, Torp-Pedersen C, Køber L. Long-term prognostic importance of diabetes after a myocardial infarction depends on left ventricular systolic function. Diabetes Care 2011; 34: 1788-1790.

17) Dziewierz A, Giszterowicz D, Siudak Z, Rakowski T, Dubiel JS, Dudek D. Admission glucose level and in-hospital outcomes in diabetic and non-diabetic patients with acute myocardial infarction. Clin Res Cardiol 2010; 99: 715-721.

18) Norhammar AM, Rydén L, Malmberg K. Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. Diabetes Care 1999; 22: 1827-1831.

19) Fava S, Aquilina O, Azzopardi J, Agius Muscat H, Fenech FF. The prognostic value of blood glucose in diabetic patients with acute myocardial infarction. Diabet Med 1996; 13: 80-83.

20) Sanjuan R, Blasco ML, Martinez-Maicas H, Carbonell N, Miñana G, Nuñez J, Bodí V, Sanchis J. Acute myocardial infarction: high risk ventricular tachyarrhythmias and admission glucose level in patients with and without diabetes mellitus. Curr Diabetes Rev 2011; 7: 126-134.

21) Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J. Diabetes, asymptomatic hyperglycemia, and 22 year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. Diabetes Care 1997; 20: 163-169.

22) Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. Diabetes Care 1999; 22: 920-924.

23) Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, Cosentino F, Jönsson B, Laakso M, Malmberg K, Priori S, Ostergren J, Tuomilehto J, Thrainsdottir I, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Deckers JW, Bertrand M, Charbonnel B, Erdmann E, Ferrannini E, Flyvbjerg A, Gohlke H, Juanatey JR, Graham I, Monteiro PF, Parhofer K, Pyörälä K, Raz I, Schernthaner G, Volpe M, Wood D; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD). Guidelines on diabetes, prediabetes, and cardiovascular diseases: executive summary. Eur Heart J 2007; 28: 88-136.

24) Skyler J. Diabetic complications: the importance of glucose control. Endocrinol Metab Clin North Am 1996; 23: 243-254.

25) Pecoraro RE, Chen MS, Porte D Jr. Glycosylated hemoglobin and fasting plasma glucose in the assessment of outpatient glycemic control in NIDDM. Diabetes Care 1982; 5: 592-599.

26) Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complication of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J 2000; 321: 405-412.