Original Article

CMJ

www.cmj.ac.kr

Glycated Hemoglobin and All-Cause Mortality in Korean Type 2 Diabetes

Mi Suk An[1], Sun A Kim[2], Jun-Ho Lee[3], Seong-Woo Choi[4], and Min-Ho Shin[2,*]

[1]Gokseong-Gun Public Health Center, Gokseong-Gun, [2]Department of Preventive Medicine, Chonnam National University Medical School, Gwangju, [3]Department of Clinical Laboratory Science, Wonkwang Health Science University, Iksan, [4]Department of Preventive Medicine, Chosun University Medical School, Gwangju, Korea

The purpose of this study was to evaluate the association between glycated hemoglobin (HbA1c) and all-cause mortality in type 2 diabetes mellitus. We conducted a community-based prospective cohort study of 352 type 2 diabetic patients aged 30-92 who participated in a community diabetes complications screening program in Gokseng-gun, Jeollanamdo, Korea. HbA1c levels were categorized as $<6.5\%$, 6.5-6.9%, 7.0-7.9%, 8.0-8.9% and $\geq 9.0\%$. Patients were followed up on for a mean of 6.9 years. The Cox proportional hazards model was used to evaluate the relationship between HbA1c levels and all-cause mortality. During the mean follow-up period of 6.9 years, 77 patients (21.9%) died. A J-shaped association was found between HbA1c and all-cause mortality, with the lowest mortality at 6.5-6.9% of HbA1c levels. Compared to patients with HbA1c of 6.5-6.9%, patients with $<6.5\%$, 7.0-7.9%, 8.0-8.9% and $\geq 9.0\%$ had an adjusted hazard ratio (95% confidence interval) for all-cause mortality of 1.71 (0.76-3.84), 1.23 (0.53-2.82), 1.32(0.51-3.44) and 2.66 (1.01-7.02), respectively. We found a J-shaped association between glycated hemoglobin and all-cause mortality in Korean type 2 diabetic patients.

Key Words: *Diabetes Mellitus; Cohort Studies; Hemoglobin A, Glycosylated; Death*

Article History:
Received August 22, 2017
Revised September 4, 2017
Accepted September 6, 2017

Corresponding Author:
Min-Ho Shin
Department of Preventive Medicine, Chonnam National University Medical School, 264 Seoyang-ro, Hwasun-eup, Hwasun 58128, Korea
Tel: +82-61-379-2621
Fax: +82-61-379-2627
E-mail: mhshinx@paran.com

INTRODUCTION

Diabetes is a major cause of premature death and disability worldwide. The prevalence of diabetes is increasing rapidly worldwide from 4.7% in 1980 to 8.5% in 2014.[1] In Korea, diabetes is the fifth most common cause of death and the age-standardized prevalence of diabetes is steadily increasing from 8.6% in 2001 to 11.0% in 2013.[2] Furthermore, Korea is ranked fourth among OECD countries in diabetes mortality.[3]

Glycemic control is very important for people with diabetes. Uncontrolled diabetes leads to complications in many organs such as chronic renal failure, blindness, cardiovascular disease and lower limb amputation.[1] Glycemic control can be assessed by the glycated hemoglobin level (HbA1c), a measure of the average glucose level over the past 2-3 months. The Diabetes Control and Complications Trial (DCCT)[4] and UK Prospective Diabetes Study (UKPDS)[5] have demonstrated that reducing HbA1c can reduce the risk of microvascular complications in type 1 and type 2 diabetes. Additionally, intensive control of type 1 diabetes patients substantially reduces the risk of cardiovascular disease outcomes.[6] However, whether or not intensive blood glucose control in type 2 diabetes can reduce the risk of macrovascular complications is controversial.[7]

To date, many cohort studies have studied the association between HbA1c levels and mortality in diabetic patients. Most of the previous studies have shown that HbA1c levels are positively associated with mortality in diabetic patients.[8] Some studies have shown nonlinear associations such as U-shaped or J-shaped associations between HbA1c and mortality.[9-11] However, to the best of my knowledge, there is no study of the association between HbA1c and mortality in diabetics in Korea. The purpose of this study was to evaluate the association between HbA1c levels and all-cause mortality in type 2 diabetes mellitus.

https://doi.org/10.4068/cmj.2017.53.3.223

MATERIALS AND METHODS

1. Subjects

Details of the study population and the baseline survey have been published previously.[12] The baseline survey was conducted in 2009 on type 2 diabetics who were enrolled in the public health center of Gokseng-gun, Jeollanamdo, Korea. The public health center registered and managed 594 diabetic patients with low incomes (less than 120% of the minimum cost of living). Almost all of the low-income diabetics in the area were enrolled in the public health center. They were invited to participate in the survey by telephone. Of these, 380 participated in the baseline survey. Twenty-eight patients were excluded from the analysis because they could not provide a blood sample or there were any missing value for covariates; therefore, the final analysis included 352 patients. The study followed the Helsinki Declaration Guidelines and obtained written consent from all subjects. The study protocol was reviewed and approved by the Institutional Review Board (I-2008-11-135).

2. Assessment of covariates

Using a structured questionnaire, well-trained interviewers collected information on cigarette smoking, alcohol consumption, exercise, duration of diabetes, antihypertensive medication, dyslipidemia medication, and any past history of cardiovascular disease. Education was categorized as elementary or higher and no education. Smoking was classified as ever smokers (current or former) and non-smokers. Alcohol consumption was classified as current drinkers and non-drinkers. Leisure time exercise was rated on a 5-point scale and dichotomized as high (very often or always) and low (never, rarely or sometimes). Weight was measured to the nearest 0.1 kg and we measured height up to the nearest 0.1 cm with light clothes without wearing shoes. Body mass index (BMI) was calculated by dividing body weight (kg) by body height (m^2). After resting for 5 minutes, blood pressure was measured twice with a standard mercury sphygmomanometer every minute and average blood pressure was used for the analysis. The concentrations of fasting glucose, creatinine, total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were measured using an automatic analyzer (HITACHI-7600, Hitachi, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) equation.[13] HbA1c levels were determined using a Bio-Rad Variant II HPLC System (Bio-Rad, Hercules, CA, USA).

Experienced medical doctors performed carotid ultrasonography with a high resolution B-mode ultrasound (SONOACE 9900, Medison, Korea). Intima-media thickness (IMT) was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. The mean carotid IMT was defined as the mean of the right and left common carotid artery IMT. Carotid plaque was defined as a focal protrusions into the lumen that were 100% thicker than the nearest area. The ankle brachial index (ABI) were measured by an automated device (VP-1000; Colin Co., Komaki, Japan). Peripheral arterial disease (PAD) was defined as having one of the ABI values less than 0.9.

3. Follow-up and ascertainment of deaths

To determine whether participants were deceased, they were followed from the date of baseline survey until death or July 31, 2016. Participants or surrogates were contacted by telephone or personal contact. For those who could not be contacted through the most recent address, Information on death status and date of death was obtained from health administrative data of the public health center.

4. Statistical analysis

Participants were divided into 5 groups according to the level of HbA1c at baseline: $<6.5\%$, 6.5-6.9%, 7.0-7.9%, 8.0-8.9% and $\geq 9.0\%$ and the characteristics of the baseline study were expressed as mean and standard deviation in the case of continuous variables, and the categorical variables were expressed in numbers and percentages. Baseline characteristics of study participants across HbA1c categories were compared using chi-square tests for categorical variables and analysis of variance for continuous variables. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for all-cause mortality. HbA1c levels of 6.5 to 6.9 was used as the referent category because there was the lowest risk of mortality at this range of HbA1c. All covariates were used sequentially as independent variables according to the following three models: age and sex were adjusted in model 1; body mass index, education level, smoking, alcohol intake and exercise were further adjusted in model 2; diabetic duration, history of hypertension, dyslipidemia, heart disease and cerebrovascular disease, systolic blood pressure, total cholesterol, HDL cholesterol, log triglyceride, eGFR, carotid IMT, carotid plaque and peripheral arterial disease were further adjusted in model 3. Age- and sex- adjusted mortality rates per 100 person-years across HbA1c categories were calculated using Poisson regression with robust variance. All tests were two-tailed and evaluated at a significance level of 0.05. All analysis was performed using STATA 14 (STATA Corp, College Station, TX).

RESULTS

The mean age of the subjects at baseline was 69.8 years and 68.5% were women. The mean duration of diabetes was 8.8 years, and mean HbA1c levels were 7.4%. During the mean follow-up period of 6.9 years, 77 patients (21.9%) died. The baseline characteristics according to HbA1c categories are shown in Table 1. Mean age gradually decreased as HbA1c levels increased, whereas diabetes duration, triglyceride levels and education attainment increased with increasing HbA1c levels. Preexisting heart disease was more common in subjects with HbA1c levels of 8.0-8.9%.

TABLE 1. Baseline characteristics according to categories of glycated hemoglobin (HbA1c)

Variables	Glycated hemoglobin (HbA1c)					p-value
	<6.5%	6.5-6.9%	7-7.9%	8-8.9%	≥9%	
Number	90	71	92	58	41	
HbA1c, %	6±0.4	6.7±0.1	7.4±0.3	8.4±0.3	10.1±1.1	<0.001
Age, years	72.7±7.4	69.7±7.8	70±9.8	68.2±9	65.4±8.8	<0.001
Sex: male	28 (31.1)	21 (29.6)	32 (34.8)	19 (32.8)	11 (26.8)	0.903
Education: elementary or higher	47 (52.2)	38 (53.5)	64 (69.6)	39 (67.2)	31 (75.6)	0.018
Ever smoking	27 (30.0)	19 (26.8)	31 (33.7)	15 (25.9)	10 (24.4)	0.754
Current alcohol consumption, %	29 (32.2)	27 (38.0)	27 (29.4)	21 (36.2)	8 (19.5)	0.297
Leisure time exercise, %	36 (40.0)	35 (49.3)	37 (40.2)	17 (29.3)	19 (46.3)	0.211
History of hypertension, %	37 (41.1)	28 (39.4)	52 (56.2)	23 (39.7)	21 (51.2)	0.108
History of dyslipidemia, %	7 (7.78)	15 (21.1)	8 (8.7)	11 (19.0)	6 (14.6)	0.050
History of heart disease, %	5 (5.6)	6 (8.5)	3 (3.3)	10 (17.2)	1 (2.4)	0.011
History of cerebrovascular disease, %	5 (5.6)	3 (4.2)	7 (7.6)	7 (12.1)	2 (4.9)	0.43
Diabetic duration, years	7±6.6	7.6±7.2	9.1±8.7	9.7±6.8	12.9±9.3	<0.001
Body mass index, kg/m^2	24.2±4	25.3±3.9	24.6±3.7	25.4±3.1	24.4±2.9	0.161
Systolic blood pressure, mmHg	130.7±18	134.1±17.2	133.1±17.6	135.2±18.9	136.7±21.2	0.406
Diastolic blood pressure, mmHg	69.9±10.4	70.6±9.3	72.5±10.2	73.7±9.6	71.9±7.7	0.135
Total cholesterol, mg/dl	188.1±36.1	196±42	198.2±45.1	197.1±41.7	206.3±49.5	0.216
Triglyceride, mg/dl	163.9±88.2	194.1±128.5	195.8±108.8	208.4±115.8	245±189.1	0.010
HDL cholesterol, mg/dl	48.9±13.5	50.3±11.9	47.4±11.1	46.8±9.4	49.4±12.1	0.405
Glucose, mg/dl	106.6±26.7	123.9±31.4	134.5±33.9	155.6±41	176.4±56.4	<0.001
GFR, mL/min/1.73 m^2						0.904
≥60	61 (67.8)	52 (73.2)	64 (69.6)	41 (70.7)	29 (70.7)	
45-59	17 (18.9)	14 (19.7)	21 (22.8)	12 (20.7)	9 (22.0)	
<45	12 (13.3)	5 (7.0)	7 (7.6)	5 (8.6)	3 (7.3)	
Carotid intima media thickness, mm	0.74±0.14	0.72±0.13	0.75±0.16	0.74±0.16	0.68±0.16	0.105
Carotid artery plaques, %	41 (45.6)	18 (25.4)	38 (41.3)	27 (46.6)	17 (41.5)	0.071
Peripheral arterial disease, %	8 (8.9)	9 (12.7)	10 (10.9)	12 (20.7)	3 (7.3)	0.20

HDL: high-density lipoprotein, GFR: glomerular filtration rate.

Fig. 1 shows a J-shaped association between HbA1c categories and age- and sex-adjusted all-cause mortality. The all-cause mortality rate per 100 person-years was the lowest at HbA1c levels of 6.5-6.9% and the highest at HbA1c levels of ≥9.0%. Table 2 summarizes the association between HbA1c categories and all-cause mortality. After adjusting for age and sex (model 1), a J-shaped association was found between HbA1c and all-cause mortality, with the lowest mortality at 6.5-6.9% of HbA1c levels. When the model was fully adjusted for potential confounding variables (model 3), the association was slightly attenuated and remained significant. Compared to patients with HbA1c of 6.5-6.9%, those with <6.5%, 7.0-7.9%, 8.0-8.9% and ≥9.0% had an increased HR (95% CI) for all-cause mortality of 1.71 (0.76-3.84), 1.23 (0.53-2.82), 1.32 (0.51-3.44) and 2.66 (1.01-7.02), respectively.

DISCUSSION

In this prospective study of type 2 diabetes, we found that a J-shaped association was observed between HbA1c levels and all-causes mortality and an excess mortality rate was observed in both low and high levels of HbA1c. In addition, the lowest risk of all-cause mortality was observed at HbA1c levels of 6.5-6.9%. This association remained after adjusting for potential confounders.

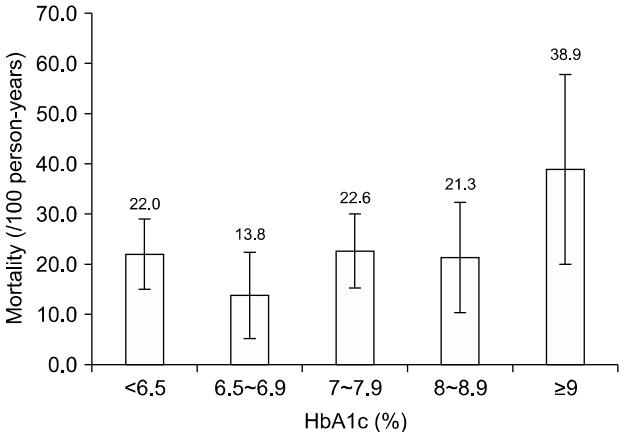

FIG. 1. Age- and sex-adjusted all-cause mortality rate according to glycated hemoglobin categories (/100 person-years).

Many observational studies have demonstrated that HbA1c levels are positively associated with mortality in diabetic patients. In a meta-analysis,[8] a 1% increase in HbA1c in patients with type 2 diabetes was associated with a 15% increase in all-cause mortality (HR 1.15, 95% CI, 1.11 to 1.20). However, in line with the findings of the present study, several studies have suggested non-linear association. Two large, retrospective cohort studies found a U-shaped association between HbA1c and mortality.[9,10] Huang et al.[9] conducted a study involving 71,092 patients with type 2 diabetes from the Kaiser Permanente Northern California and found that the mortality rate was lowest in patients with HbA1c of 7-7.9% (HR 0.83, 95% CI, 0.76 to 0.90) compared with those with HbA1c <6.0% and highest in those with HbA1c ≥11.0% (HR 1.31, 95% CI, 1.09-1.57). Currie et al.[10] conducted a study involving 27,965 patients with type 2 diabetes in the UK General Practice Research Database and found a U-shaped association, with the lowest mortality risk at about 7.5% of HbA1c levels. In another study of type 1 diabetic patients, Schoenaker et al.,[11] found a U-shaped association with nadir at HbA1c 8.1%. Nonlinear associations obtained from observational studies are also consistent with the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[14] in which there was an increase in mortality in the intensive arm targeting HbA1c levels of less than 6%. In addition, there was no reduction in cardiovascular events with intensive glycemic control in two randomized controlled studies.[15,16]

The potential mechanism underlying the association between low HbA1c and increased all-cause mortality remains unclear. The association between low HbA1c and higher mortality may be explained by hypoglycemia as the most common adverse effect of diabetes treatment and residual confounding by comorbidities. First, previous studies have shown that lower HbA1c levels are associated with higher risk of hypoglycemia which is associated with unfavorable health outcomes. A recent meta-analysis reported that severe hypoglycemia represents about twice the risk of cardiovascular disease.[17] In the DCCT, severe hypoglycemia risk increased more than threefold in the intensive diabetes therapy group 4. In the Diabetes and Aging Study, Lipska et al.[18] found that there was a higher

TABLE 2. Association between categories of glycated hemoglobin and all-cause mortality

HbA1c, %	No.	Number of deaths	Model 1	Model 2	Model 3
<6.5%	90	24	1.91 (0.88-4.12)	1.70 (0.78-3.72)	1.71 (0.76-3.84)
6.5-6.9%	71	9	1.00 (reference)	1.00 (reference)	1.00 (reference)
7-7.9%	92	22	1.78 (0.82-3.88)	1.37 (0.61-3.07)	1.23 (0.53-2.82)
8-8.9%	58	11	1.69 (0.70-4.08)	1.40 (0.57-3.42)	1.32 (0.51-3.44)
≥9%	41	11	3.48 (1.44-8.45)	2.99 (1.21-7.33)	2.66 (1.01-7.02)

Data are hazard ratio (95% confidence intervals). Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, body mass index, education level, smoking, alcohol intake and exercise. Model 3 was further adjusted for diabetic duration, history of hypertension, dyslipidemia, heart disease and cerebrovascular disease, systolic blood pressure, total cholesterol, log triglyceride, HDL cholesterol, estimated glomerular filtration rate, carotid intima-media thickness, carotid plaque and peripheral arterial disease.

risk of hypoglycemia in patients with near-normal glycemia (HbA1c $<6\%$) and those with poor glycemic control (HbA1c $\geq 9\%$). In the ACCORD study, the risk of severe hypoglycemia was higher in the intensive treatment group compared to the standard treatment group.[14] However, because of the lack of information on hypoglycemia in the baseline study of this study, it was not possible to compare the difference in hypoglycemic experience between the HbA1c groups. Furthermore, comorbid conditions may be a confounding factor. Older diabetic patients with low HbA1c levels may suffer from poor nutritional status, frailty, or sarcopenia.[9] In a study of non-diabetic subjects, participants with low HbA1c values had elevated mean cell volume, ferritin, and liver function measures which may increase all-cause mortality.[19] Greenfield et al found that type 2 diabetic patients with multiple comorbidities may receive diminished cardiovascular benefits with intensive blood glucose control.[20] This possibility is also supported by previous population-based studies that have shown a nonlinear association between HbA1c levels and all-cause mortality in adults without diabetes.[19,21-23] Data from the Atherosclerosis Risk in Communities study showed a J-shaped relationship between HbA1c and mortality in people without diabetes.[22] Similarly, a study conducted using the nationwide German National Health Interview and Examination Survey showed a U-shaped association, with the lowest mortality at HbA1c levels of 5.4-5.6% and an excess mortality at $\leq 5.0\%$ and $\geq 6.4\%$.[23] Another study from the US National Health and Nutrition Examination Survey showed an inverted J-shaped association.[19] In their study, compared with HbA1c levels of 5.0-5.4%, very low HbA1c ($<4.0\%$) was associated with a higher all-cause mortality risk (HR, 2.90; 95% CI, 1.25 to 6.76). Although the present study adjusted for many potential confounders related to some comorbid conditions, the possibility of residual confounding from comorbid conditions that were not measured could not excluded.

The main strength of this study is the cohort design. To the best of my knowledge, this is the first study to evaluate the association between HbA1c and mortality in diabetic patients in Korea. In addition, the strengths of this study further derive from that fact that it includes data on a wide range of potential confounders. However, this study had several limitations. First, because this is an observational study, the possibility that there were differences among the two groups other than the difference in HbA1c levels cannot be completely excluded. Second, study subjects were restricted to low socioeconomic status which limits generalizability of study findings to other patient populations. Third, changes in glycemic control may contribute to the change in hazard ratio over time. However, we were only able to measure HbA1c at baseline only and could not measure the changes over time. Fourth, we evaluated only all-cause mortality and we could not perform cause-specific mortality analysis.

In conclusion, J-shaped relationships were found between HbA1c levels and over-all mortality in Korean type 2 diabetic patients. Further research is needed to determine the causal mechanisms linking low HbA1c levels and mortality.

ACKNOWLEDGEMENTS

This manuscript is a revision of the first author' master' thesis from Chonnam National University.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. World Health Organization. Global report on diabetes. Geneva, Switzerland:World Health Organization,2016.
2. Ha KH, Kim DJ. Trends in the diabetes epidemic in Korea. Endocrinol Metab (Seoul) 2015;30:142-6.
3. Organisation for Economic Co-operation and Development. Health at a glance : Asia/Pacific, 2010. Paris:OECD Publishing, 2010.
4. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
5. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321:412-9.
6. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643-53.
7. American Diabetes Association. Standards of medical care in Diabetes-2016 abridged for primary care providers. Clin Diabetes 2016;34:3-21.
8. Zhang Y, Hu G, Yuan Z, Chen L. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with type 2 diabetes: a systematic review and meta-analysis. PLoS One 2012;7:e42551.
9. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care 2011;34:1329-36.
10. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481-9.
11. Schoenaker DA, Simon D, Chaturvedi N, Fuller JH, Soedamah-Muthu SS; EURODIAB Prospective Complications Study Group. Glycemic control and all-cause mortality risk in type 1 diabetes patients: the EURODIAB prospective complications study. J Clin Endocrinol Metab 2014;99:800-7.
12. Choi SW, Shin MH, Yun WJ, Kim HY, Lee YH, Kweon SS, et al. Association between hemoglobin A1c, carotid atherosclerosis, arterial stiffness, and peripheral arterial disease in Korean type 2 diabetic patients. J Diabetes Complications 2011;25:7-13.

13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
14. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.
15. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.
16. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
17. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ 2013;347:f4533.
18. Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, Krumholz HM, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the diabetes and aging study. Diabetes Care 2013;36:3535-42.
19. Carson AP, Fox CS, McGuire DK, Levitan EB, Laclaustra M, Mann DM, et al. Low hemoglobin A1c and risk of all-cause mortality among US adults without diabetes. Circ Cardiovasc Qual Outcomes 2010;3:661-7.
20. Greenfield S, Billimek J, Pellegrini F, Franciosi M, De Berardis G, Nicolucci A, et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: a cohort study. Ann Intern Med 2009;151:854-60.
21. de Vegt F, Dekker JM, Ruhé HG, Stehouwer CD, Nijpels G, Bouter LM, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn study. Diabetologia 1999;42:926-31.
22. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800-11.
23. Paprott R, Schaffrath Rosario A, Busch MA, Du Y, Thiele S, Scheidt-Nave C, et al. Association between hemoglobin A1c and all-cause mortality: results of the mortality follow-up of the German National Health Interview and Examination Survey 1998. Diabetes Care 2015;38:249-56.