International Journal of Cardiology 266 (2018) 250–253

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Impact of optimal glycemic control on the progression of coronary artery calcification in asymptomatic patients with diabetes

Ki-Bum Won [a,b], Donghee Han [b], Ji Hyun Lee [b], Sang-Eun Lee [b], Ji Min Sung [b], Su-Yeon Choi [c], Eun Ju Chun [d], Sung Hak Park [e], Hae-Won Han [f], Jidong Sung [g], Hae Ok Jung [h], Hyuk-Jae Chang [b,*]

[a] Division of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea
[b] Division of Cardiology, Yonsei Cardiovascular Center, Yonsei University Health System, South Korea
[c] Division of Cardiology, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, South Korea
[d] Division of Radiology, Seoul National University Bundang Hospital, Seongnam, South Korea
[e] Division of Radiology, Gangnam Heartscan Clinic, Seoul, South Korea
[f] Department of Internal Medicine, Gangnam Heartscan Clinic, Seoul, South Korea
[g] Division of Cardiology, Heart Stroke & Vascular Institute, Samsung Medical Center, Seoul, South Korea
[h] Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

ARTICLE INFO

*Article history:*
Received 31 October 2017
Received in revised form 19 February 2018
Accepted 23 March 2018

*Keywords:*
Diabetes mellitus
Optimal glycemic control
Coronary artery calcification

ABSTRACT

*Background:* Data on the impact of optimal glycemic control (OGC) on the progression of coronary artery calcification, an important marker for future adverse cardiovascular events in individuals with diabetes are limited.
*Methods:* We investigated 1637 asymptomatic adults with diabetes (56 ± 8 years, 88.8% men) and no history of coronary artery disease or stroke, who underwent serial coronary artery calcium (CAC) screening. The median inter-scan period was 3.0 (2.0–4.4) years. The change in CAC was compared base on OGC status. OGC was defined as a follow-up hemoglobin A1C (HbA1C) of <7.0%, and CAC progression was defined by a square root (√) transformed difference between the baseline and follow-up CAC scores (Δ √transformed CAC) of ≥2.5.
*Results:* Despite no significant difference in the baseline CAC scores, the incidence of CAC progression was lower in the OGC group than in the non-OGC group (45.4% vs. 51.7%; $p < 0.013$). The two groups differed in the Δ √transformed (OGC, 3.8 ± 6.4; non-OGC, 4.7 ± 6.9; $p = 0.016$) and annualized Δ √transformed CAC (OGC, 1.1 ± 2.4; non-OGC, 1.4 ± 2.6; $p = 0.010$) scores. Subgroup analysis showed that OGC significantly reduced the risk of CAC progression in patients aged <65 years and in: smokers, and patients with a body mass index of <25 kg/m$^2$, dyslipidemia, and baseline CAC scores between 1–100 and >400. In multivariate regression analysis, OGC was independently associated with a reduced risk of CAC progression (odds ratio, 0.745, 95% confidence interval, 0.601–0.924; $p = 0.007$).
*Conclusion:* OGC attenuated the progression of coronary artery calcification in asymptomatic patients with diabetes.


## 1. Introduction

Diabetes is strongly associated with an increased risk of cardiovascular (CV) morbidity and mortality worldwide. It is associated with a two- to three-fold increase in the risk of coronary artery disease [1,2]. Previous epidemiologic data have indicated that poor glycemic control is associated with an increased risk of major CV events [3–5]. Recently, several long-term follow-up studies on patients with diabetes have reported that intensive glucose control is effective for reducing adverse CV outcomes [6,7]. Thus, in clinical practice, the significance of optimal glycemic control (OGC) is emphasized in patients with diabetes.

Coronary artery calcium (CAC) is closely associated with coronary atherosclerotic burden and CV events [8–10]. Moreover, CAC progression has an additive predictive value for mortality compared with baseline CAC scores and traditional CV risk factors [11]. However, limited data are available on the impact of OGC on CAC progression in patients with diabetes. Therefore, the present study aims to evaluate the impact of OGC on CAC progression in asymptomatic patients with diabetes by using serial cardiac computed tomography (CT).

## 2. Methods

### 2.1. Study population and design

Data from the Korea Initiatives on Coronary Artery Calcification (KOICA) multicenter registry were analyzed. This is a retrospective, single-ethnicity, multicenter observational registry in a self-referral setting for patients who underwent health checkups at six healthcare centers in South Korea. In total, 93,707 patients were enrolled in the KOICA

* Corresponding author at: Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei University Health System, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea.
*E-mail address:* hjchang@yuhs.ac (H.-J. Chang).

https://doi.org/10.1016/j.ijcard.2018.03.112
0167-5273/

registry from December 2012 to August 2016. Self-reported medical questionnaires were used to obtain information about patients' medical history. All data were obtained during the healthcare center checkup visit. Among the 93,707 patients from this registry, 1637 patients with established diabetes and available follow-up HbA1C level data, and who underwent at least two CAC CT scan examinations, were included in the present study. All patients were categorized into two groups based on a HbA1C cut-off value of 7.0%. Diabetes mellitus (DM) was defined by a fasting glucose level of ≥126 mg/dL, HbA1C level of ≥6.5%, referral diagnosis of DM, or currently receiving antidiabetic treatment [12,13]. OGC was defined as a follow-up HbA1C of <7.0%. Body mass index (BMI) was calculated as weight (kg) ÷ height ($m^2$). All blood samples were obtained after a minimum of 8-h fast and analyzed for triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and glucose levels. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or treatment with antihypertensive agents. Dyslipidemia was defined as total cholesterol ≥240 mg/dL, LDL ≥130 mg/dL, HDL ≤40 mg/dL, and triglycerides ≥150 mg/dL and/or treatment with lipid-lowering agents. The appropriate institutional review board committees for each healthcare center have approved the study protocol. CAC progression was defined as the square root (√) transformed difference between the baseline and follow-up CAC scores (Δ √transformed CAC score) of ≥2.5, considering inter-scan variability [14]. In all centers, CAC scans were obtained using a >16-slice multi-detector CT scanner (GE 64-slice Lightspeed, Philips Brilliance 256 iCT, Philips Brilliance 40 channel MDCT, and Siemens 16-slice Sensation). All centers utilized standard prospective or retrospective methods. The CAC score was evaluated based on the scoring system from a previously described method [15].

### 2.2. Statistical analysis

Continuous variables are expressed as means ± standard deviations. Categorical variables are presented as absolute values and proportions. Continuous variables were compared using Student's *t*-test. Categorical variables were compared using the $\chi^2$-test or Fisher's exact test, as appropriate. To identify the impact of OGC on CAC progression, subgroup analysis was performed. Univariate logistic regression analysis was performed to identify the significant clinical factors for CAC progression. Then, multivariate logistic regression analysis was performed to identify the independent predictors for CAC progression after adjusting for all independent variables in the univariate analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences version 19 (SPSS, Chicago, IL), and $p < 0.05$ was considered significant for all analyses.

## 3. Results

### 3.1. Baseline characteristics

The mean age of the patients in this study was 56 ± 8 years, and 1453 (88.8%) patients were men. Among them, 1036 (63.3%) and 601 (36.7%) were categorized into OGC and non-OGC groups. In addition, 825 (79.6%) and 380 (63.2%) participants were initially under the same condition in OGC and non-OGC group, respectively. Table 1 describes the baseline characteristics of patients. At enrollment in the present study, the mean ages, BMIs, waist circumferences, and triglyceride levels were significantly higher in the non-OGC group than those in the OGC group. However, the incidence of hypertension was significantly higher in the OGC group than that in the non-OGC group.

### 3.2. Change in CAC according to OGC status

Table 2 presents the baseline and follow-up CAC scores on OGC status. The median inter-scan period was 3.0 (2.0–4.4) years. The baseline CAC score and categorical CAC score were not significantly different between the two groups. The incidence of CAC progression was significantly lower in the OGC group than that in the non-OGC group (OGC, 45.4%; non-OGC, 51.7%; $p = 0.013$). Both the Δ √transformed (OGC, 3.8 ± 6.4; non-OGC, 4.7 ± 6.9; $p = 0.016$) and annualized Δ √transformed CAC score (OGC, 1.1 ± 2.4; non-OGC, 1.4 ± 2.6; $p = 0.010$) were different between the two groups. The annualized Δ CAC score was also significantly lower in the OGC group than that in the non-OGC group (OGC, 31 ± 108; non-OGC, 44 ± 139; $p = 0.048$). In the OGC group, the incidence of CAC progression was significantly higher in patients with initial HbA1C of ≥7.0% than in those with initial HbA1C <7.0%. However, no significant difference in the incidence of CAC progression was observed in the non-OGC group (Supplementary Fig. 1).

**Table 1**
Baseline characteristics.

| | OGC ($n = 1036$) | Non-OGC ($n = 601$) | *p* |
|---|---|---|---|
| Age, yrs | 56 ± 8 | 55 ± 8 | 0.003 |
| Male, *n* (%) | 916 (88.4) | 537 (89.4) | 0.564 |
| BMI, kg/$m^2$ | 25.1 ± 2.9 | 25.5 ± 2.9 | 0.018 |
| Waist circumference, cm | 89 ± 8 | 90 ± 8 | 0.002 |
| Systolic blood pressure, mmHg | 123 ± 16 | 122 ± 16 | 0.456 |
| Diastolic blood pressure, mmHg | 76 ± 10 | 76 ± 11 | 0.326 |
| Hypertension, *n* (%) | 613 (60.0) | 292 (50.3) | <0.001 |
| Dyslipidemia, *n* (%) | 790 (76.3) | 456 (75.9) | 0.862 |
| Non-smoking, *n* (%) | 259 (27.0) | 139 (25.7) | 0.596 |
| Initial laboratory findings | | | |
| Total cholesterol, mg/dL | 189 ± 36 | 190 ± 38 | 0.683 |
| Triglycerides, mg/dL | 146 ± 81 | 170 ± 116 | <0.001 |
| HDL cholesterol, mg/dL | 52 ± 17 | 49 ± 15 | <0.001 |
| LDL cholesterol, mg/dL | 114 ± 34 | 115 ± 32 | 0.492 |
| Calcium, mg/dL | 9.1 ± 0.4 | 9.2 ± 0.4 | 0.157 |
| Phosphate, mg/dL | 3.3 ± 0.6 | 3.4 ± 0.6 | 0.283 |
| Creatinine, mg/dL | 1.0 ± 0.2 | 0.9 ± 0.2 | 0.065 |
| Fasting glucose, mg/dL | 119 ± 27 | 145 ± 40 | <0.001 |
| HbA1C, % | 6.4 ± 0.9 | 7.5 ± 1.2 | <0.001 |

Values are given as mean ± standard deviation or number (%).
BMI = body mass index; HbA1C = hemoglobin A1C; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGC = optimal glycemic control.

### 3.3. Subgroup analysis for the impact of OGC on CAC progression

Fig. 1 shows the subgroup analysis of the estimated odds ratio (OR) of OGC for CAC progression. OGC was significantly associated with a reduced risk of CAC progression in patients aged <65 years (OR, 0.788; 95% confidence interval [CI], 0.634–0.978; $p = 0.031$) and smokers (OR, 0.769; 95% CI, 0.602–0.984; $p = 0.036$), as well as those with a BMI of <25 kg/$m^2$ (OR, 0.650; 95% CI, 0.483–0.874; $p = 0.004$), dyslipidemia (OR, 0.791; 95% CI, 0.628–0.997; $p = 0.047$), and baseline categorical CAC scores of 0–100 (OR, 0.736; 95% CI, 0.585–0.926; $p = 0.009$) and > 400 (OR, 0.397; 95% CI, 0.182–0.866; $p = 0.020$).

### 3.4. Association between clinical factors and CAC progression

Univariate logistic regression analysis showed that age (OR, 1.027; 95% CI, 1.015–1.039; $p < 0.001$), male sex (OR, 1.732; 95% CI, 1.260–2.381; $p = 0.001$), and baseline CAC scores of >100 (OR, 1.678; 95% CI, 1.329–2.119; $p < 0.001$) were associated with an increased risk of CAC progression. However, OGC (OR, 0.774; 95% CI, 0.633–0.947; $p = 0.013$) was associated with a reduced risk of CAC progression. In multivariate logistic regression analysis, age (OR, 1.032; 95% CI, 1.018–1.047;

**Table 2**
Change in CAC according by glycemic control status.

| | OGC ($n = 1036$) | Non-OGC ($n = 601$) | *p* |
|---|---|---|---|
| Baseline | | | |
| CAC score | 109 ± 313 | 112 ± 326 | 0.843 |
| Categorical CAC score | | | 0.714 |
| 0–100 | 798 (77.0) | 466 (77.5) | |
| 101–400 | 168 (16.2) | 90 (15.0) | |
| >400 | 70 (6.8) | 45 (7.5) | |
| Follow-up | | | |
| CAC score | 212 ± 393 | 244 ± 467 | 0.166 |
| Categorical CAC score | | | 0.091 |
| 0–100 | 615 (59.4) | 348 (58.0) | |
| 101–400 | 262 (25.3) | 136 (22.7) | |
| >400 | 159 (15.3) | 116 (19.3) | |
| Δ CAC score | 103 ± 283 | 132 ± 297 | 0.060 |
| Annualized Δ CAC score | 31 ± 108 | 44 ± 139 | 0.048 |
| Δ √transformed CAC score | 3.8 ± 6.4 | 4.7 ± 6.9 | 0.016 |
| Annualized Δ √transformed CAC score | 1.1 ± 2.4 | 1.4 ± 2.6 | 0.010 |
| CAC progression, *n* (%) | 470 (45.4) | 311 (51.7) | 0.013 |

CAC was defined as Δ √transformed CAC score ≥ 2.5, considering inter-scan variability.
CAC = coronary artery calcium; OGC = optimal glycemic control.

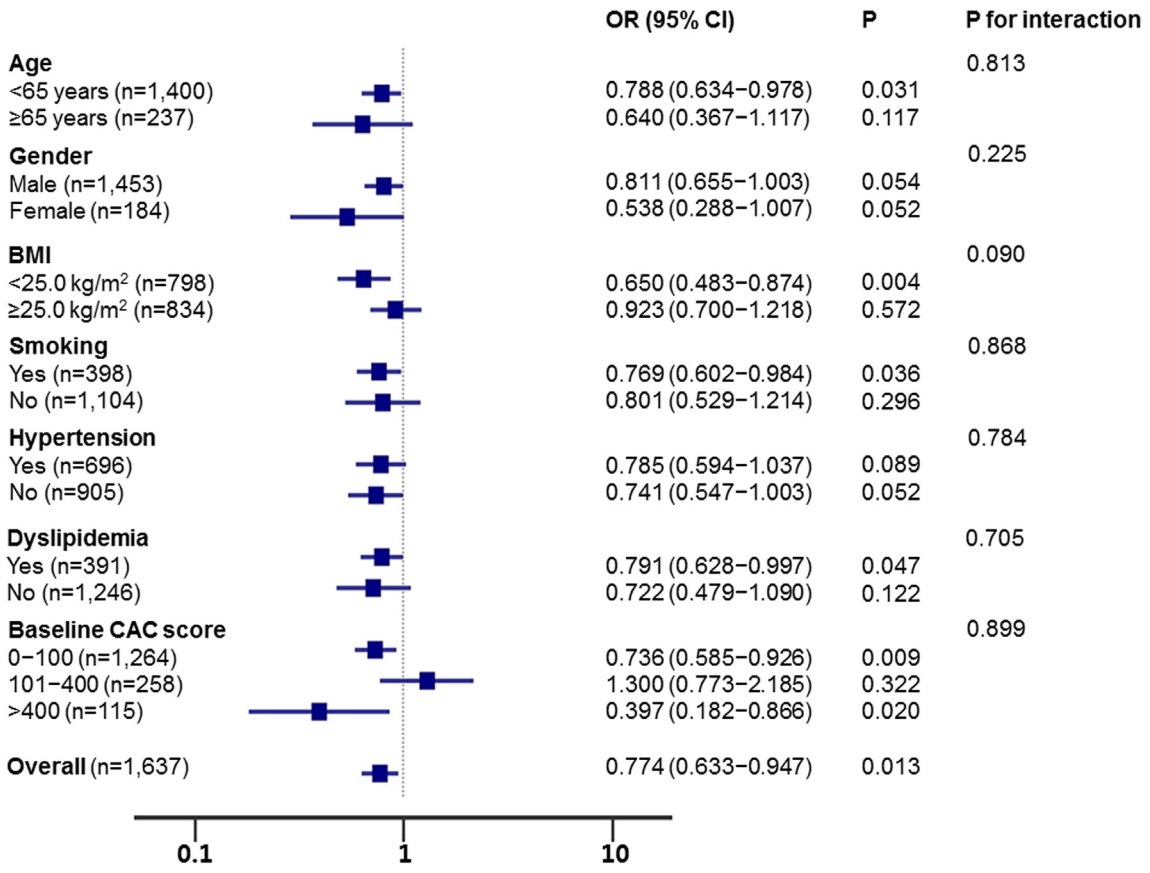


**Fig. 1.** Subgroup analysis of the impact of OGC on CAC progression.

$p < 0.001$), male sex (OR, 1.866; 95% CI, 1.255–2.775; $p = 0.002$), and OGC (OR, 0.756; 95% CI, 0.609–0.939; $p = 0.011$) were independent determinants of CAC progression (Table 3). In addition, OGC was significantly associated with a Δ CAC score > 200 (OR, 0.660; 95% CI, 0.494–0.881; $p = 0.005$) and Δ CAC score > 300 (OR, 0.621; 95% CI, 0.448–0.861; $p = 0.004$) after adjusting for confounding factors (Supplementary Table 1).

## 4. Discussion

The major finding of this longitudinal study was that OGC was independently associated with a reduced risk of CAC progression in asymptomatic patients with diabetes. In addition, this beneficial impact of OGC on CAC progression was more prominent in diabetic patients with traditional CV risk factors such as smoking, dyslipidemia, and a baseline categorical CAC score of >400.

**Table 3**
Logistic regression analyses for identifying the impact of clinical variables on CAC progression.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Age, years | 1.027 (1.015–1.039) | <0.001 | 1.032 (1.018–1.047) | <0.001 |
| Male | 1.732 (1.260–2.381) | 0.001 | 1.866 (1.255–2.775) | 0.002 |
| BMI, kg/m$^2$ | 1.028 (0.994–1.064) | 0.105 | 1.033 (0.995–1.074) | 0.093 |
| Non-smoking | 0.798 (0.633–1.005) | 0.055 | 0.873 (0.669–1.140) | 0.318 |
| Hypertension | 1.010 (0.829–1.231) | 0.919 | 0.915 (0.735–1.139) | 0.424 |
| Dyslipidemia | 1.021 (0.813–1.282) | 0.858 | 0.973 (0.758–1.250) | 0.832 |
| Baseline CAC score > 100 | 1.678 (1.329–2.119) | <0.001 | 1.287 (0.989–1.676) | 0.061 |
| OGC | 0.774 (0.633–0.947) | 0.013 | 0.756 (0.609–0.939) | 0.011 |

CAC was defined as Δ √transformed CAC score ≥ 2.5, considering inter-scan variability.
BMI = body mass index; CAC = coronary artery calcium; CI = confidence interval; LDL = low-density lipoprotein; OR = odds ratio.

CAC score is an independent predictor of coronary events and improves CV risk prediction in asymptomatic patients [16,17]. Moreover, a recent study revealed that CAC progression has an additive predictive value for adverse clinical outcomes, as compared with baseline CAC scores and traditional CV risk factors [11]. Considering that noncalcified obstructive plaques were scarcely observed in asymptomatic patients with diabetes [18], identifying clinical factors that affect CAC progression may be an important issue in asymptomatic diabetes populations. Recent clinical studies have suggested that achieving OGC status might be important to prevent adverse clinical events in patients with established diabetes [6,7]. However, the relationship between glycemic control status and CAC progression has rarely been investigated in asymptomatic patients with diabetes.

Anand et al. reported that baseline CAC severity and suboptimal glycemic control was significantly associated with an increased risk of CAC progression in 398 patients with diabetes and without prior coronary disease or symptoms [19]. Recently, the Heinz Nixdorf Recall study, a population-based cohort study in Germany, also reported that CAC progression was stronger in patients with established diabetes and poor glycemic control [20]. In the present study, we obtained consistent results that OGC was independently associated with a reduced risk of CAC progression. However, a baseline CAC score of >100 was not associated with CAC progression after adjusting for confounding factors in this study. Previous clinical and experimental studies have suggested that coronary calcification in intimal atherosclerosis lesions might induce further inflammation and calcification through a positive feedback loop [21,22]. Notably, OGC inhibited CAC progression in diabetic patients with a baseline CAC score of >400. This might imply that OGC could reverse the negative effect of baseline coronary artery calcification on CAC progression in patients with diabetes. Considering the previous

result from the Veterans Affairs Diabetes Trial, that intensive glucose-lowering therapy reduced CV events in diabetic patients with less extensive calcified coronary atherosclerosis [23], further large prospective studies are necessary to identify whether the inhibition of CAC progression could reduce adverse clinical outcomes in diabetic patients with heavy calcified coronary lesions.

Despite the substantial impact of diabetes on coronary artery calcification, its pathogenesis remains incompletely understood. One of the most important mechanisms in patients with diabetes is hyperglycemic damage, mainly driven by the accumulation of free radicals, which activates vascular inflammation and endothelial dysfunction. Also, hyperglycemia itself also increases oxidative stress by increasing glucose oxidation [24]. This strongly supports the significance of achieving OGC to prevent CAC progression. Data on the effect of OGC on metabolic problems have not been limited. However, most patients with diabetes, approximately 65%–85%, have concomitant metabolic abnormalities [25,26]. Subgroup analysis in the present study showed that OGC significantly reduced the risk of CAC progression in patients with diabetes aged <65 years, smokers, and those with BMI of <25 kg/m$^2$ and dyslipidemia. Although the beneficial effects of OGC were not significant in other subgroups, this tendency was consistent in most subgroups. The size of the categories may impact $p$ values, which should be taken into account for the interpretation of the data. In addition, further investigation of this issue in multi-ethnic populations might be necessary because clinical features of diabetes differ by ethnicity [27].

A recent study using serial coronary intravascular ultrasound reported that statins promote coronary atheroma calcification, independent of their plaque-regressive effects [28]. However, the association between lipid profiles and CAC progression in subjects with diabetes has been unconfirmed. In the present study, the follow-up levels of triglycerides and HDL were significantly different based on OGC status (Supplementary Table 2). Unlike the follow-up OGC status, the follow-up levels of total cholesterol, triglycerides, HDL, and LDL were not significantly associated with CAC progression after adjusting for confounding factors (Supplementary Table 3). To address this issue, prospective studies with larger sample sizes of patients with established diabetes might be required.

The present study had several limitations. First, the present study had a retrospective design based on an asymptomatic population who underwent health checkups in healthcare centers. In addition, the population was comprised of self-referred subjects. Thus, the results may have been influenced by unobserved confounders or potential selection biases. Second, because of the observational design of the study, we could not eliminate the possible effects of medications for hypertension, dyslipidemia, and diabetes on the progression of coronary artery calcification. Third, we could not adjust physical activity status because of the paucity of relevant data. Fourth, longitudinal HbA1C control between CAC scans could not be confirmed because only baseline and final HbA1C data were available. Finally, the present study only included a Korean population. Nevertheless, this study uniquely identified the association between OGC and CAC progression after adjusting traditional CV risk factors in asymptomatic diabetic patients.

In conclusion, OGC was associated with a reduced risk of CAC progression in asymptomatic patients with diabetes. This beneficial effects of OGC were observed in diabetic patients with heavy calcific coronary lesions.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.03.112.

## Competing interests

The authors declare that they have no competing interests.

## Acknowledgments

This research was supported by the Leading Foreign Research Institute Recruitment Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (No. 2012027176).

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