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Longitudinal assessment of coronary plaque volume change related to glycemic status using serial coronary computed tomography angiography: A PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) substudy

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ABSTRACT

Background: Data on the impact of glycemic status on coronary plaque progression have been limited. This study evaluated the association between glycemic status and coronary plaque volume change (PVC) using coronary computed tomography angiography (CCTA).

Methods: A total of 1296 subjects (61 ± 9, 56.9% male) who underwent serial CCTA with available glycemic status were enrolled and analyzed from the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry. The median inter-scan period was 3.2 (2.6–4.4) years. Quantitative assessment of coronary plaques was performed at both scans. All participants were categorized into the following groups according to glycemic status: normal, pre-diabetes (pre-DM), and diabetes mellitus (DM).

Results: During the follow-up, significant differences in PVC (normal: 51.3 ± 83.3 mm^3 vs. pre-DM: 51.0 ± 84.3 mm^3 vs. DM: 72.6 ± 95.0 mm^3; $p < 0.001$) and annualized PVC (normal: 14.9 ± 24.9 mm^3 vs. pre-DM: 15.7 ± 23.8 mm^3 vs. DM: 21.0 ± 27.7 mm^3; $p = 0.001$) were observed among the 3 groups. Compared with normal individuals, individuals with pre-DM showed no significant differences in the adjusted odds ratio (OR) for plaque progression (PP) (1.338, 95% confidence interval [CI] 0.967–1.853; $p = 0.079$). However, the adjusted OR for PP was higher in DM individuals than in normal individuals (1.635, 95% CI 1.126–2.375; $p = 0.010$).

Conclusion: DM had an incremental impact on coronary PP, but pre-DM appeared to have no significant association with an increased risk of coronary PP after adjusting for confounding factors.

Clinical trial registration: ClinicalTrials.gov NCT02803411.

Abbreviations

CAD	coronary artery disease
CCTA	coronary computed tomography angiography
CI	confidence interval
CV	cardiovascular
DM	diabetes mellitus
HbA1C	hemoglobin A1C
OR	odds ratio
PP	plaque progression
Pre-DM	pre-diabetes
PVC	plaque volume change

1. Introduction

Diabetes mellitus (DM) is strongly associated with increasing risk of cardiovascular (CV) disease and adverse clinical outcomes.[1–3] Several meta-analyses have revealed that DM imparted a 2- to 3-fold increase in the risk of developing coronary artery disease (CAD).[4–6] However, data on the association between pre-diabetes (pre-DM) and the risk of CAD are limited in general population. Although a large cross-sectional study has suggested that DM but not pre-DM is related to increased risk for subclinical coronary atherosclerosis,[7] data on the natural history of coronary atherosclerosis according to glycemic status have been limited. Recently, compared with invasive methods, improved technology in coronary computed tomography angiography (CCTA) has allowed for the non-invasive assessment of coronary atherosclerosis with high-diagnostic performance.[8,9] Therefore, the present study used serial CCTA to evaluate the change of coronary plaque volume along the full length of the coronary vascular tree according to glycemic status.

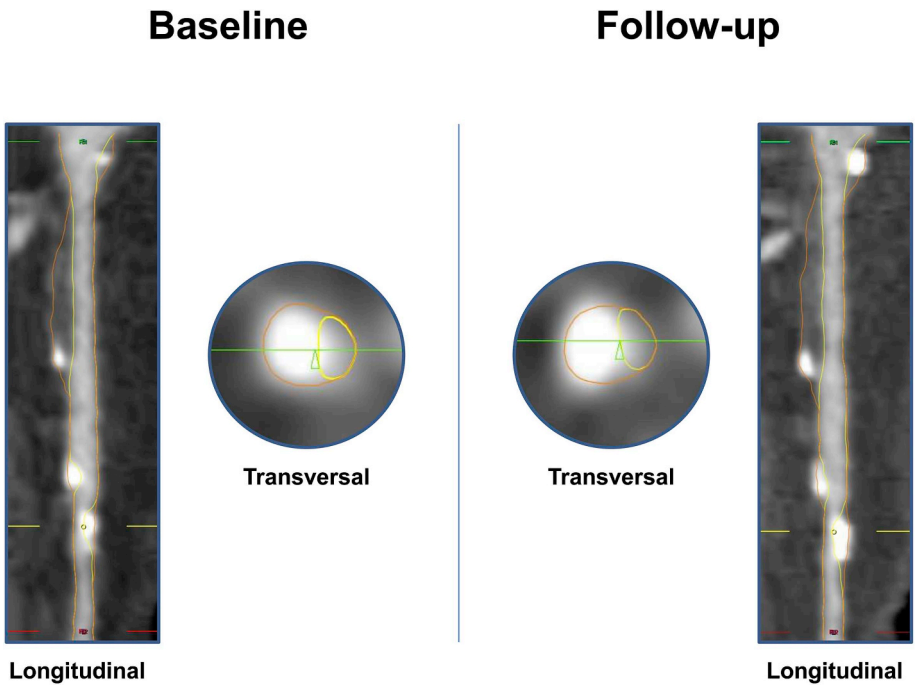

Fig. 1. Representative Image for the measurement of coronary plaque.

2. Methods

2.1. Design overview, setting, and participants

The overall study design of the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry has been previously described.[10] PARADIGM is a prospective, open-label, international, multicenter dynamic observational registry designed to evaluate associations between changes in serial CCTA imaging findings and clinical presentation. Between 2003 and 2015, a total of 2252 consecutive subjects underwent CCTA at 13 centers in 7 countries. All subjects who participated in PARADIGM underwent 2 or more clinically indicated CCTAs using 64-detector rows or greater for CAD evaluation with at least a 2-year interval between the baseline and follow-up CCTA. Among 2252 consecutive participants, 1296 subjects with available glycemic data were included in the present study. All participants were categorized into 3 groups according to glycemic status: normal (n = 469), pre-DM (n = 440), and DM (n = 387). Pre-DM was defined as a fasting plasma glucose of 100–125 mg/dL or hemoglobin A1C (HbA1C) levels 5.7–6.4%.[11] DM was defined as either fasting glucose ≥126 mg/dL, HbA1C levels ≥6.5%, a referral diagnosis of diabetes, or antidiabetic treatment.[11,12] The study protocol was approved by the institutional review boards of all centers, and when required, all patients provided written informed consent.

2.2. Acquisition and interpretation of CCTA

All testing, data acquisition, and image post-processing for CCTA were in accordance with Society of Cardiovascular Computed Tomography guidelines.[13,14] CCTA was conducted using a scanner with ≥64-detector rows in all centers. Baseline and follow-up datasets from each center were transferred to an offline workstation for analysis using semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9.1; Medis Medical Imaging Systems, Leiden, the Netherlands) with manual correction. Independent level III–experienced readers who were masked to the clinical and test results analyzed all CCTAs. Segments with a diameter ≥2 mm were evaluated using a modified 17-segment American Heart Association model for coronary segment classification.[14,15] Segments were matched between baseline and follow-up CCTA using branch points as landmarks. For longitudinal comparisons of CCTAs, both baseline and follow-up coronary segments were co-registered using fiduciary landmarks, including distance from ostia or branch vessels takeoffs. Plaque volumes (mm^3) of all coronary segments were obtained and then summated to generate the total plaque volume on a per-patient level. Plaque volume change (PVC) was defined as plaque volume at follow-up minus plaque volume at baseline in per-patient level. Annualized PVC was defined as PVC divided by inter-scan period. Coronary plaque progression (PP) was defined as the difference in plaque volume between follow-up and baseline CCTA > 0. Atherosclerotic plaque volume was further subclassified by composition, employing pre-defined intensity cutoff values in Hounsfield units (HU) for necrotic core (−30 to 30 HU), fibro-fatty plaque (31–130 HU), fibrous plaque (131–350 HU), and calcified plaque (≥351 HU).[16,17] Representative CCTA imaging is presented in Fig. 1.

2.3. Statistical analysis

Continuous variables are expressed as the mean ± SD or medians and interquartile range. Categorical variables are presented as absolute values and proportions. The continuous variables across the 3 glycemic groups were compared using one-way analysis of variance with Bonferroni's post hoc test or Kruskal-Wallis test for continuous variables, as appropriate. Categorical variables were compared using a chi-square test. Univariate and multivariate logistic regression analysis was performed to identify the independent predictors of PP. Variables with $p < 0.05$ in the univariate analysis were considered confounding variables and entered into multivariate logistic regression analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences version 19 (SPSS, Chicago, Illinois), and a p value < 0.05 was considered significant for all analyses.

3. Results

3.1. Baseline characteristics

The mean age of participants was 61 ± 9 years, and 738 (56.9%) were male. Of the participants, 469 (36.2%), 440 (34.0%), and 387 (29.8%) were categorized as normal, pre-DM, and DM, respectively. The baseline characteristics of participants according to glycemic status

Table 1
Baseline clinical characteristics.

	Normal (n = 469)	Pre-DM (n = 440)	DM (n = 387)	p
Age, years	61 ± 10	61 ± 9	62 ± 9 *†	0.019
Male, n (%)	261 (55.7)	243 (55.2)	234 (60.5)	0.246
Body mass index, kg/m^2	24.5 ± 3.1	25.2 ± 3.1 *	25.5 ± 3.5 *	< 0.001
Systolic blood pressure, mmHg	125 ± 16	127 ± 17	128 ± 17 *	0.027
Diastolic blood pressure, mmHg	77 ± 10	77 ± 11	77 ± 11	0.503
Hypertension, n (%)	247 (52.9)	254 (57.7)	272 (70.3)	< 0.001
Dyslipidemia, n (%)	144 (30.8)	160 (36.4)	173 (44.7)	< 0.001
Smoking, n (%)	175 (37.5)	184 (41.8)	170 (44.0)	0.135
Total cholesterol, mg/dL	185 ± 38	189 ± 36	173 ± 40 *†	< 0.001
Triglyceride, mg/dL	133 ± 83	146 ± 79 *	151 ± 87 *	0.005
High-density lipoprotein, mg/dL	50 ± 13	49 ± 13	47 ± 12 *	0.005
Low-density lipoprotein, mg/dL	116 ± 36	116 ± 31	101 ± 34 *†	< 0.001
Creatinine, mg/dL	1.0 ± 0.7	1.0 ± 0.6	1.0 ± 0.4	0.821
Fasting glucose, mg/dL	90 ± 6	104 ± 10 *	142 ± 50 *†	< 0.001
HbA1C, %	5.4 ± 0.2	5.8 ± 0.2 *	7.5 ± 1.3 *†	< 0.001
Medications, n (%)				
Beta-blockers	143 (30.8)	129 (29.3)	148 (38.3) *†	0.013
Calcium channel blockers	125 (27.0)	115 (26.2)	152 (39.5) *†	< 0.001
ACEIs/ARBs	143 (30.8)	130 (29.6)	174 (45.2) *†	< 0.001
Diuretics	42 (9.1)	42 (9.6)	47 (12.2)	0.278
Statins	198 (44.4)	190 (44.6)	211 (56.7) *†	< 0.001

Values represent the mean ± standard deviation or number (%).
ACEIs = Angiotensin-converting enzyme inhibitors; ARBs = Angiotensin receptor blockers; DM = diabetes mellitus.
*p < 0.05 vs. normal, †p < 0.05 vs. pre-diabetes.

are described in Table 1. Compared with normal, both pre-DM and DM participants had significantly higher body mass index and triglyceride levels. Age was higher but the levels of total and low-density lipoprotein cholesterol were lower in DM participants than in both normal and pre-DM participants (all $p < 0.05$). There was a significant difference in the incidence of hypertension and dyslipidemia, but no significant difference in the incidence of male gender and smoking among all 3 groups. Baseline coronary characteristics according to glycemic status at baseline CCTA are present in Table 2. Median inter-scan period was 3.2 (2.6–4.4) years. There were significant differences in the lesion length, vessel volume, lumen volume, and plaque volume among the 3 groups.

3.2. Plaque volume changes according to glycemic status

The results of changes in coronary plaque volume according to glycemic group are presented in Fig. 2. A significant difference in PVC observed among the 3 groups (normal: 51.3 ± 83.3 mm^3 vs. pre-DM: 51.0 ± 84.3 mm^3 vs. DM: 72.6 ± 95.0 mm^3; $p < 0.001$). Compared with normal participants, pre-DM participants showed no significant differences in PVC ($p = 0.999$). However, the PVC was significantly higher in DM participants than in both normal and pre-DM participants ($p < 0.05$, respectively). Similarly, the annualized PVC was significantly different among the 3 groups (normal: 14.9 ± 24.9 mm^3 vs. pre-DM: 15.7 ± 21.0 mm^3 vs. DM: 21.0 ± 27.7 mm^3; $p = 0.001$). There was no significant difference in annualized PVC changes between normal participants and pre-DM participants ($p = 0.999$). However, the annualized PVC was significantly higher in DM participants than in both normal and pre-DM participants ($p < 0.05$, respectively).

3.3. Association between glycemic status and coronary PP

Univariate logistic regression analysis showed that age (odds ratio [OR]: 1.036, 95% confidential interval [CI]: 1.021–1.051; $p < 0.001$), male gender (OR: 1.597, 95% CI: 1.222–2.086; $p = 0.001$), body mass index (OR: 1.091, 95% CI: 1.044–1.141; $p < 0.001$), smoking (OR: 1.705, 95% CI: 1.284–2.263; $p < 0.001$), hypertension (OR: 1.999, 95% CI: 1.528–2.616; $p < 0.001$), dyslipidemia (OR: 1.603, 95% CI: 1.200–2.142; $p = 0.001$), and baseline plaque volume (OR: 1.007, 95% CI: 1.006–1.009; $p < 0.001$) were significantly associated with increased risk of coronary PP. Compared with the normal group, the pre-DM (OR: 1.435, 95% CI: 1.056–1.950; $p = 0.021$) and DM (OR: 2.290, 95% CI: 1.614–3.250; $p < 0.001$) groups had an increased risk of coronary PP. In the multivariate logistic regression analysis, there was no significant difference in the adjusted OR of pre-DM participants for PP compared with that of normal participants (1.338, 95% CI: 0.967–1.853; $p = 0.079$). However, the adjusted OR for PP was higher in DM participants than in normal participants (1.635, 95% CI: 1.126–2.375; $p = 0.010$) (Table 3). The relationship of glycemic status to the progression of coronary plaque sub-types is described in Table 4.

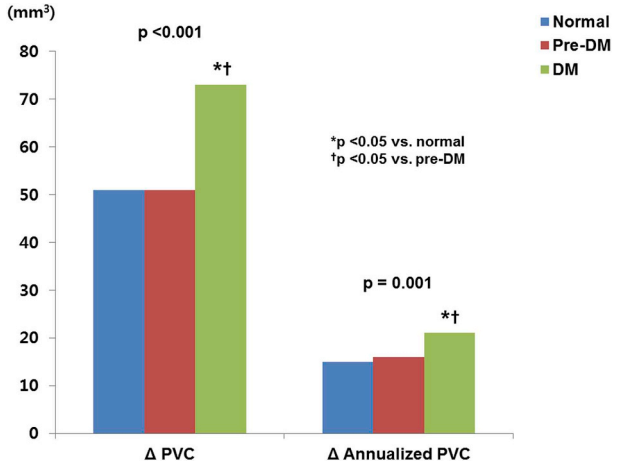

Fig. 2. Coronary plaque volume changes according to glycemic status.

4. Conclusions

The present study evaluated the natural history of coronary atherosclerosis related to glycemic status in subjects with low-to-intermediate risk. The main finding of this study is that pre-DM, unlike DM, is not independently associated with an increased risk of coronary PP during a short-term period.

The COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry (CONFIRM) previously revealed that DM was strongly associated with increased prevalence, extent, and severity of CAD using CCTA.[18] However, the relationship between pre-DM and CAD was inconsistent.[19,20] Recently, quantitative CCTA has been proven to be a useful non-invasive tool to evaluate the progression of coronary atherosclerosis.[21] In the present study, traditional risk factors including age, body mass index, smoking, and hypertension had a significant impact on the increase of coronary plaque volume over time. Compared with individuals with normal glycemic status, DM was independently associated with increased coronary plaque volume, but pre-DM did not have a significant impact on coronary PP after adjusting for confounding factors.

Despite different clinical features of DM according to ethnicity,[22] individuals with DM exhibit multiple concomitant metabolic abnormalities.[23,24] Both the European Society of Cardiology and American College of Cardiology/American Heart Association recommend stricter lipid-lowering therapy, especially for low-density lipoprotein cholesterol, in subjects with established DM.[25,26] In the present study, we observed that DM subjects had significantly lower levels of low-density lipoprotein cholesterol than did both normal and pre-DM subjects according to current guidelines. However, annualized PVC was significantly higher in DM subjects than in both normal and pre-DM subjects. This finding might imply that strict lipid lowering therapy might be insufficient to prevent coronary PP in DM subjects. Recently, several studies reported the effectiveness of intensive glucose control

Table 2
Baseline lesion characteristics.

	Normal (n = 469)	Pre-DM (n = 440)	DM (n = 387)	p
Lesion length, mm	373.1 (277.7–441.1)	388.5 (295.5–476.2) *	365.8 (241.2–443.5)†	0.001
Vessel volume, mm^3	1890.6 (1324.5–2542.1)	2038.5 (1427.5–2837.9) *	1883.0 (1193.7–2496.3)†	0.012
Lumen volume, mm^3	1773.0 (1252.5–2475.4)	1925.8 (1321.3–2707.7) *	1761.3 (1097.1–2382.3)†	0.006
Plaque volume, mm^3	35.4 (0.0–125.0)	40.8 (5.1–141.5)	77.3 (22.6–175.3) *†	< 0.001
Fibrous	16.7 (0.0–57.1)	18.8 (2.3–59.7)	31.5 (9.0–77.6) *†	< 0.001
Fibrous-fatty	2.3 (0.0–20.0)	2.8 (0.0–19.1)	7.4 (0.3–32.0) *†	< 0.001
Necrotic-core	0.0 (0.0–1.0)	0.0 (0.0–0.09)	0.1 (0.0–2.5) *†	< 0.001
Dense calcium	3.1 (0.0–33.1)	7.4 (0.0–40.8) *	15.7 (0.8–55.6) *†	< 0.001

Values are median (interquartile range). DM = diabetes mellitus. *$p < 0.05$ vs. normal, †$p < 0.05$ vs. pre-diabetes.

Table 3
Association between clinical variables and coronary PP.

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age, years	1.036 (1.021–1.051)	< 0.001	1.022 (1.005–1.039)	0.010
Male	1.597 (1.222–2.086)	0.001	1.255 (0.923–1.706)	0.147
Body mass index, kg/m^2	1.091 (1.044–1.141)	< 0.001	1.060 (1.011–1.113)	0.016
Smoking	1.705 (1.284–2.263)	< 0.001	1.430 (1.035–1.977)	0.030
Hypertension	1.999 (1.528–2.616)	< 0.001	1.354 (1.005–1.824)	0.046
Dyslipidemia	1.603 (1.200–2.142)	0.001	1.283 (0.941–1.748)	0.115
Baseline plaque volume, mm^3	1.007 (1.006–1.009)	< 0.001	1.006 (1.004–1.008)	< 0.001
Glycemic status				
Normal	1	–	1	–
Pre-DM	1.435 (1.056–1.950)	0.021	1.338 (0.967–1.853)	0.079
DM	2.290 (1.614–3.250)	< 0.001	1.635 (1.126–2.375)	0.010

CI = confidence interval; DM = diabetes mellitus; OR = odds ratio; PP = plaque progression.

Table 4
Relationship of glycemic status to the progression of coronary plaque sub-types.

	Fibrous		Fibrous-fatty		Necrotic-core		Dense calcium	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Normal	1	–	1	–	1	–	1	–
Pre-DM	1.052 (0.799–1.384)	0.720	1.355 (1.032–1.779)	0.029	1.115 (0.833–1.492)	0.464	1.114 (0.806–1.541)	0.512
DM	1.328 (0.988–1.786)	0.060	1.330 (1.000–1.770)	0.050	1.399 (1.038–1.885)	0.028	1.648 (1.127–2.411)	0.010

CI = confidence interval; DM = diabetes mellitus; OR = odds ratio.
Adjusted for age, male sex, body mass index, smoking, hypertension, and dyslipidemia.

for reducing adverse CV outcomes.[27,28] These results suggest that coronary atherosclerotic progression is closely linked to chronic exposure to hyperglycemia. Thus, strict glycemic control might be emphasized to prevent or delay coronary PP in DM subjects. In addition, further prospective studies are required to address this issue.

The concept of metabolic syndrome, a cluster of metabolic disorders with representative of insulin resistance, has been advocated as a useful clinical tool to predict the development of DM and CV disease.[29] A previous cohort study reported that metabolic syndrome had an incremental impact on subclinical atherosclerosis in subjects without established DM.[30] Another cross-sectional study reported that pre-DM, unlike established DM, was not associated with an increased risk of subclinical coronary atherosclerosis.[7] Considering the impact of metabolic disorders on adverse CV outcomes,[31,32] both controlling concomitant metabolic abnormalities and early detecting the development of DM might be important in subjects with pre-DM.

The present study has some limitations. First, data on the oral glucose tolerance test were not available in the present study. Second, participants with pre-DM had a near upper limit normal HbA1C levels which was, on average, in absolute values not significantly different from normal. Third, the inter-scan period was somewhat short to judge the impact of glycemic status on the progression of coronary atherosclerosis. Fourth, larger plaque volumes at baseline might lead to larger increases in plaque volume. However, we evaluated the association between glycemic status and coronary PP after adjustment for baseline plaque volume. Fifth, we could not confirm the glycemic status on small coronary artery in the present study. Finally, despite the application of strict and standardized criteria for the CCTA assessment, atherosclerosis findings might be influenced by the Hounsfield unit density. Despite these limitations, this study used serial CCTA to estimate plaque volume change in a large cohort of multi-ethnic subjects and identified the impact of glycemic status on coronary PP beyond traditional CV risk factors.

In conclusion, DM had an incremental impact on coronary PP, but pre-DM appeared to have no significant association with an increased risk of coronary PP after adjusting for confounding factors.

Conflicts of interest

None.

Author contributions

K.-B.W and S.-E.L drafted the manuscript. K.-B.W and J.M.S analyzed and interpreted the data. S.-E.L., B.K.L., H.-B.P., R.H., A.R., M.H., Y.-J.K., E.C., D.A., G.P., M.J.B., I.G., E.J.C., F.C., E.M., H.M., J.A.L., S.S., J.H.C., R.V., H.S., K.C., G.R., P.H.S., D.S.B., J.N., L.J.S., and J.J.B. acquired the data. J.K.M. and H.-J.C. made critical revision of the manuscript for important intellectual content.

Disclosure

All authors have no conflicts of interest/financial disclosure.

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References

1. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes.* 1994;43:960–967.
2. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339:229–234.
3. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation.* 1999;100:1134–1146.
4. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care.* 2000;23:962–996 8.
5. Kanaya AM, Grady D, Barrett-Connor E. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis.

Arch Intern Med. 2002;162:1737–1745.
6. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ.* 2006;332:73–77 8.
7. Park GM, Cho YR, Lee SW, et al. Prediabetes is not a risk factor for subclinical coronary atherosclerosis. *Int J Cardiol.* 2017;243:479–484.
8. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med.* 2008;359:2324–2336.
9. Weustink AC, Mollet NR, Neefjes LA, et al. Diagnostic accuracy and clinical utility of noninvasive testing for coronary artery disease. *Ann Intern Med.* 2010;152:630–639.
10. Lee SE, Chang HJ, Rizvi A, et al. Rationale and design of the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry: a comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter serial coronary computed tomographic angiography study. *Am Heart J.* 2016;182:72–79.
11. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care.* 2014;37(Suppl. 1):S14–S80.
12. Furusyo N, Koga T, Ai M, Otokozawa S, et al. Utility of glycated albumin for the diagnosis of diabetes mellitus in a Japanese population study: results from the Kyushu and Okinawa Population Study (KOPS). *Diabetologia.* 2011;54:3028–3036.
13. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr.* 2014;8:342–358.
14. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography guidelines committee: endorsed by the north American society for cardiovascular imaging (NASCI). *J Cardiovasc Comput Tomogr.* 2016;10:435–449.
15. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol.* 2015;66:337–346.
16. de Graaf MA, Broersen A, Kitslaar PH, et al. Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. *Int J Cardiovasc Imag.* 2013;29:1177–1190.
17. Achenbach S, Moselewski F, Ropers D, et al. Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography a segment-based comparison with intravascular ultrasound. *Circulation.* 2004;109:14–17.
18. Rana JS, Dunning A, Achenbach S, et al. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluatioN for Clinical Outcomes): an InteRnational Multicenter Registry. *Diabetes Care.* 2012;35:1787–1794.
19. Pankow JS, Kwan DK, Duncan BB, et al. Cardiometabolic risk in impaired fasting glucose and impaired glucose tolerance: the Atherosclerosis Risk in Communities Study. *Diabetes Care.* 2007;30:325–331.
20. Levitzky YS, Pencina MJ, D'Agostino RB, et al. Impact of impaired fasting glucose on cardiovascular disease: the Framingham Heart Study. *J Am Coll Cardiol.* 2008;51:264–270.
21. Shin S, Park HB, Chang HJ, et al. Impact of intensive LDL cholesterol lowering on coronary artery atherosclerosis progression: a serial CT angiography study. *JACC Cardiovasc Imaging.* 2017;10:437–446.
22. Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. *Lancet.* 2006;368:1681–1688.
23. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes.* 2003;52:1210–1214.
24. Tong PC, Kong AP, So WY, et al. The usefulness of the international diabetes federation and the national cholesterol education Program's adult treatment panel III definitions of the metabolic syndrome in predicting coronary heart disease in subjects with type 2 diabetes. *Diabetes Care.* 2007;30:1206–1211.
25. Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J.* 2013;34:3035–3087.
26. Stone NJ, Robinson JG, Lichtenstein AH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;2014(63):2889–2934.
27. Hayward RA, Reaven PD, Wiitala WL, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2015;372:2197–2206.
28. Orchard TJ, Nathan DM, Zinman B, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *J Am Med Assoc.* 2015;313:45–53.
29. Simmons RK, Alberti KG, Gale EA, et al. The metabolic syndrome: useful concept or clinical tool? report of a WHO expert consultation. *Diabetologia.* 2010;53:600–605.
30. Won KB, Chang HJ, Kim HC, et al. Differential impact of metabolic syndrome on subclinical atherosclerosis according to the presence of diabetes. *Cardiovasc Diabetol.* 2013;12:41.
31. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *J Am Med Assoc.* 2002;288:2709–2716.
32. McNeill AM, Rosamond WD, Girman CJ, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care.* 2005;28:385–390.