Metabolism Clinical and Experimental 101 (2019) 153991

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Risk of coronary artery disease according to glucose abnormality status and prior coronary artery disease in Japanese men

Masaru Kitazawa [a], Kazuya Fujihara [a,*], Taeko Osawa [a], Masahiko Yamamoto [a], Mayuko Harada Yamada [a,b], Masanori Kaneko [a], Yasuhiro Matsubayashi [a], Takaho Yamada [a], Nauta Yamanaka [c], Hiroyasu Seida [c], Hirohito Sone [a]

[a] Department of Internal Medicine, Niigata University Faculty of Medicine, Niigata, Japan
[b] Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
[c] JMDC Inc., Tokyo, Japan

ARTICLE INFO

Article history:
Received 29 May 2019
Accepted 21 September 2019
Available online xxxx

Keywords:
Coronary artery disease
Glucose abnormality status
Clinical epidemiology
Cardiovascular disease
Risk factors

ABSTRACT

Objective: Although glucose abnormality status (GAS), prior coronary artery disease (CAD), and other traditional risk factors affect the incidence of subsequent CAD, their impact in the same cohort has been scantly studied.
Research design and methods: We analyzed data from a nationwide claims database in Japan that was accumulated during 2008–2016 involving 138,162 men aged 18–72 years. Participants were classified as having normoglycemia, borderline glycemia, or diabetes mellitus (DM) with prior CAD (CAD+) or without prior CAD (CAD−). Cox regression model identified variables related to the incidence of CAD.
Results: Among CAD−, management of traditional risks differed from those with and without subsequent CAD events. On the other hand, such differences were weaker in borderline glycemia and DM CAD+, and the influence of traditional risk factors on subsequent CAD was not observed. Cox regression model showed that borderline glycemia and DM confer approximately 1.2- and 2.8-fold excess risks of CAD, respectively, compared with CAD− with normoglycemia. CAD+ confers approximately a 5- to 8-fold increased risk. The impacts of DM and prior CAD additively reached a hazard ratio (HR) of 15.74 (95% confidence interval [CI]: 11.82–21.00). However, the HR in those with borderline glycemia and CAD+ was 7.20 (95% CI: 5.01–10.34), which was not different from those with normoglycemia and CAD+.
Conclusion: Control status of traditional risk factors and impact on subsequent CAD differ among categories of glycemic status with and without prior CAD. Individualizing treatment strategies is needed in consideration of risk factors, such as GAS and CAD+.

1. Introduction

Coronary artery disease (CAD) is known to predispose patients with diabetes to a lower quality of life as well as higher rates of cardiovascular mortality. Although it is well established that both prior CAD [1] and diabetes [2–6] are known predictors of subsequent CAD, previous studies did not exclude borderline glycemia from the non-diabetic category, resulting in overestimating the risk of non-diabetes.

The risk of incident CAD greatly differs depending on the presence of prior CAD in diabetic patients [3,7]. In addition, people with diabetes have higher mortality rates after acute myocardial infarction than those without diabetes [8]. Recently, the presence of prior CAD has been regarded as an important determinant in the selection of glucose-lowering medications in managing hyperglycemia as recommended by the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) [9].

The prevalence of borderline glycemia is 7%, 16%, and 13% in the world, United States, and Japan, respectively [10]. As with diabetes, borderline glycemia is associated with an increased risk of cardiovascular disease [11,12]. Although it is known that the risk of CAD differs according to various risk factors, such as a metabolically unhealthy status and age [13,14], it has yet to be clarified whether the risk of CAD differs according to the presence of prior CAD in individuals with borderline glycemia as is the case with diabetes. Therefore, we investigated the impact of the presence of prior CAD, glucose abnormality status and their combinations on the incidence of CAD using large-scale claims data.

Abbreviations: CAD, coronary artery disease; HRs, hazard ratios; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

* Corresponding author at: Niigata University Faculty of Medicine, Department of Internal Medicine, 1-754 Asahimachi, Niigata, Niigata 951-8510, Japan.
E-mail address: kafujihara-dm@umin.ac.jp (K. Fujihara).

https://doi.org/10.1016/j.metabol.2019.153991
0026-0495/

2. Materials and methods

2.1. Study participants

The present study analyzed data from a nationwide claims-based database that included 296,504 people who belong to a health insurance provider for company employees and their dependents in Japan [15]. Men aged 18–72 years who had been followed for at least 3 years between 1 April 2008 and 31 March 2013 were included and followed up to 31 August 2016. Excluded were women (n = 107,398), those who were not followed for at least 3 years, and those with no health examination data including blood test results (n = 50,944). Finally, data were analyzed on 138,162 men. More complete details of the study were described elsewhere [14,16–19].

2.2. Definitions

Participants were classified as having normoglycemia, borderline glycemia defined by fasting plasma glucose (FPG) and HbA1c, or diabetes based on FPG, HbA1c, and claims database data as follows: normoglycemia, both FPG <5.6 mmol/L and HbA1c <42 mmol/mol and no antidiabetic drug prescription; borderline glycemia defined by FPG and HbA1c, either FPG 5.6–6.9 mmol/L or HbA1c 42–50 mmol/mol or both and no antidiabetic drug prescription; and diabetes, FPG ≥7.0 mmol/L or HbA1c ≥51 mmol/mol or both and no antidiabetic drug prescription or with an antidiabetic drug prescription regardless of FPG or HbA1c. Participants who had prior CAD events at baseline and subsequent CAD events were determined according to claims using International Classification of Disease 10th revision (ICD-10) codes for cardiac events and medical procedures and questionnaires.

2.3. Statistical analysis

Categorical variables were expressed as numerals and percentages and were compared with χ^2 tests. Continuous variables were expressed as the mean ± standard deviations or median and interquartile range. Continuous variables were compared using the unpaired Student's *t*-test or the Mann-Whitney *U* test for two-group comparisons based on their distributions. Cox regression model identified variables related to the incidence of CAD. Covariates included traditional CAD risk factors in each model. To directly compare the effect of risk factors that have different units or means, we calculated the hazard ratio (HR) per 1-SD increment for several variables. Analyses were performed using SPSS (version 19.0, Chicago, IL, USA). Statistical significance was considered for $P < 0.05$. The Ethics Committee of Niigata University approved this study.

3. Results

Baseline characteristics of our study participants according to glucose abnormality category and prior CAD are shown in Table 1. Among 138,162 participants, 78,230, 45,610, and 14,322 had normoglycemia, borderline glycemia, and diabetes, respectively. In each glucose category, 963, 868, and 709, respectively, had prior CAD (CAD+). Median follow-up duration was 5.0 years. During the study period, 234, 291, and 348 CAD events occurred in participants with normoglycemia, borderline glycemia, and diabetes, respectively. The rates of CAD were 0.53, 1.14, and 3.93 per 1000 person-years in those with normoglycemia, borderline glycemia, and diabetes, respectively, in those with no prior CAD (CAD−) and 7.00, 8.93, and 24.47 per 1000 person-years, respectively, in those with CAD+.

LDL-C level and smoking were well controlled in the CAD+ groups, and BMI was well controlled in CAD− regardless of the glucose

Table 1
Characteristics of study participants according to glucose abnormality category and prior CAD.

	Normoglycemia			Borderline glycemia			Diabetes		
	Prior CAD		P	Prior CAD		P	Prior CAD		P
	(−)	(+)		(−)	(+)		(−)	(+)	
	n = 77,267	n = 963		n = 44,742	n = 868		n = 13,613	n = 709	
Age (years)	43 ± 9	48 ± 8	<0.01	47 ± 8	52 ± 7	<0.01	51 ± 8	55 ± 7	<0.01
BMI (kg/m^2)	22.9 ± 2.9	23.3 ± 3	<0.01	24.1 ± 3.3	24.7 ± 3.4	<0.01	25.8 ± 4.1	26.1 ± 3.8	0.02
SBP (mm Hg)	120 ± 14	121 ± 14	0.03	124 ± 15	125 ± 15	0.11	130 ± 16	128 ± 16	<0.01
DBP (mm Hg)	75 ± 11	77 ± 11	<0.01	78 ± 11	79 ± 10	0.22	81 ± 11	79 ± 11	<0.01
HbA1c (mmol/mol) n = 136,228	34.1 ± 2.7	34.6 ± 2.6	<0.01	38.7 ± 3.4	39.5 ± 3.3	<0.01	55.1 ± 15.7	53.6 ± 13.3	<0.01
FPG (mmol/L) n = 136,553	4.92 ± 0.37	4.91 ± 0.38	0.51	5.57 ± 0.54	5.61 ± 0.62	0.04	8.04 ± 2.43	7.82 ± 2.41	0.02
LDL-C (mmol/L)	3.1 ± 0.8	3.0 ± 0.8	<0.01	3.3 ± 0.8	3.1 ± 0.8	<0.01	3.3 ± 0.8	2.9 ± 0.8	<0.01
HDL-C (mmol/L)	1.54 ± 0.38	1.53 ± 0.38	0.62	1.49 ± 0.38	1.46 ± 0.37	0.61	1.41 ± 0.37	1.35 ± 0.35	<0.01
Triglycerides (mmol/L)	2.4 (1.7–3.5)	2.6 (1.8–3.8)	<0.01	2.9 (2.0–4.3)	2.9 (2.1–4.3)	0.12	3.4 (2.3–5.0)	3.0 (2.1–4.4)	0.48
Current smoking (%)	29,530 (38.2%)	285 (29.6%)	<0.01	17,600 (39.3%)	271 (31.2%)	<0.01	5858 (43.0%)	195 (27.5%)	<0.01
History of dyslipidemia	31,336 (40.6%)	503 (52.2%)	<0.01	25,042 (56.0%)	583 (67.2%)	<0.01	9719 (71.4%)	607 (85.6%)	<0.01
History of hypertension	11,223 (14.5%)	355 (36.9%)	<0.01	11,557 (25.8%)	448 (51.6%)	<0.01	6477 (47.6%)	555 (78.3%)	<0.01
Medications									
β-Blockers	514 (0.7%)	111 (11.5%)	<0.01	739 (1.7%)	149 (17.2%)	<0.01	527 (3.9%)	228 (32.2%)	<0.01
ACEs and ARBs	3050 (3.9%)	186 (19.3%)	<0.01	3513 (7.9%)	249 (28.7%)	<0.01	3256 (23.9%)	424 (59.8%)	<0.01
CCBs	2833 (3.7%)	172 (17.9%)	<0.01	3534 (7.9%)	209 (24.1%)	<0.01	2683 (19.7%)	282 (39.8%)	<0.01
Diuretics	408 (0.5%)	31 (3.2%)	<0.01	539 (1.2%)	50 (5.8%)	<0.01	459 (3.4%)	91 (12.8%)	<0.01
Statins	2285 (3.0%)	182 (18.9%)	<0.01	2901 (6.5%)	266 (30.6%)	<0.01	2948 (21.7%)	447 (63.0%)	<0.01
Antiplatelet agents	322 (0.4%)	200 (20.8%)	<0.01	403 (0.9%)	246 (28.3%)	<0.01	424 (3.2%)	430 (60.6%)	<0.01
OHAs							6171 (45.3%)	479 (67.6%)	<0.01
GLP-1							65 (0.5%)	6 (0.8%)	0.17
Insulin							1067 (7.8%)	82 (11.6%)	<0.01
Rate per 1000 person-years	0.53	7.00		1.14	8.93		3.93	24.47	

Data are presented as n (%), mean ± SD or median (interquartile range); International Federation of Clinical Chemistry and Laboratory Medicine units.
CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; LDL-C/HDL-C, low-density/high-density lipoprotein cholesterol, ACEs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin-receptor blockers; CCBs calcium-channel blockers; OHAs, oral hypoglycemic agents; GLP-1, glucagon-like peptide 1 receptor agonists.
Hypertension was defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg, or treatment for hypertension.
Dyslipidemia was defined as LDL-C >3.6 mmol/L, HDL-C <1.0 mmol/L, triglycerides >3.9 mmol/L or treatment for dyslipidemia.

Table 2
Cox regression analysis of variables for incidence of coronary artery disease (CAD) according to glucose abnormality category and prior CAD.

	Normoglycemia		Borderline glycemia		Diabetes	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Prior CAD− Prior CAD+	Ref 8.79 (5.98–12.92)	<0.01	Ref 5.46 (3.82–7.80)	<0.01	Ref 6.51 (4.98–8.52)	<0.01
Prior CAD− Prior CAD+	Ref Ref		1.19 (0.98–1.44) 0.97 (0.59–1.60)	0.07 0.92	2.60 (2.13–3.18) 1.88 (1.17–3.01)	<0.01 <0.01
Prior CAD− Prior CAD+	Ref 9.90 (6.77–14.47)	<0.01	1.24 (1.03–1.50) 7.20 (5.01–10.34)	0.03 <0.01	2.75 (2.25–3.36) 15.74 (11.82–20.95)	<0.01 <0.01
Prior CAD− Prior CAD+	0.36 (0.30–0.44) 3.60 (2.47–5.25)	<0.01 <0.01	0.45 (0.38–0.54) 2.62 (1.84–3.71)	<0.01 <0.01	Ref 5.72 (4.41–7.42)	<0.01 <0.01

Each variable for CAD adjusted by age, body mass index, systolic blood pressure, low-density lipoprotein-C, high density lipoprotein-C, and current smoking.

abnormality category. In those with normoglycemia, SBP, DBP, TG, and HbA1c were well controlled in the CAD− group compared with the CAD+ group. Control status of these risk factors was improved with progression of glucose abnormality in the CAD+ group. In fact, the numbers of risk factors that have statistical difference were decreased in borderline glycemia and diabetes compared to normoglycemia. In those with borderline glycemia, SBP, DBP, and TG levels were not significantly different between CAD− and CAD+, unlike in those with normoglycemia. In those with diabetes, SBP, DBP, and HbA1c were well controlled in the CAD+ group. The prevalence of statin use increased across groups according to glucose abnormality and CAD+.

In the CAD− groups, control status of traditional cardiovascular risk factors differed according to subsequent CAD events. On the other hand, in participants with borderline glycemia and diabetes in the CAD+ groups, the differences were weakened. Only the HDL-C level was lower in people with CAD events, whereas the control status of BMI, SBP, HbA1c, FPG, LDL-C, and TG levels and the proportion of current smoking were similar in those groups (Supplemental Table 1).

Table 2 shows the multivariate-adjusted HRs for CAD events according to glucose abnormality category and CAD+. Although diabetes presented almost a 2-fold risk for CAD events regardless of prior CAD, the influence of borderline glycemia on CAD was modest and was less in CAD+ than in CAD−. The CAD+ groups had approximately 5- to 8-fold increases in CAD events regardless of glucose abnormality category. The impacts of diabetes and prior CAD on future CAD events were additive reaching 15.74 (95% confidence interval [CI]: 11.82–21.00). Conversely, the HR of those with borderline glycemia and CAD+ was 7.20 (95% CI: 5.01–10.34), which was not different from those with normoglycemia and CAD+. Participants with CAD+ without diabetes had an approximately 3-fold significantly higher increase in CAD events than CAD− diabetic participants.

Table 3 shows the HRs of each variable on future CAD according to the presence of prior CAD and glucose abnormality category. In the CAD− group, the effects of almost all traditional risk factors, such as age, current smoking, BMI, SBP, LDL-C, and HDL-C, on future CAD was statistically significant regardless of the glucose abnormality category. In the CAD+ group, those impacts were weakened, especially in borderline glycemia and diabetes. Only HDL-C was significantly associated with future CAD events in individuals with diabetes and CAD+.

4. Discussion

This is the first study to evaluate the impact of glucose abnormality status, prior CAD, and their combinations on subsequent CAD in the same cohort. Prior CAD and diabetes confer approximately 5- to 8-fold and 2.8-fold subsequent CAD risks, respectively, whereas the impact

Table 3
Cox regression analysis of variables for incidence of CAD according to prior CAD and glucose abnormality category.

	Prior CAD (−)						Prior CAD (+)					
	Normoglycemia		Borderline glycemia		Diabetes		Normoglycemia		Borderline glycemia		Diabetes	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.12 (1.10–1.14)	<0.01	1.11 (1.09–1.13)	<0.01	1.05 (1.03–1.07)	<0.01	1.09 (1.03–1.14)	<0.01	1.08 (1.03–1.13)	<0.01	0.99 (0.96–1.02)	0.59
Current smoking	1.43 (1.08–1.89)	<0.01	2.17 (1.68–2.80)	<0.01	1.41 (1.11–1.81)	<0.01	1.11 (0.49–2.54)	0.80	1.12 (0.56–2.28)	0.74	1.09 (0.67–1.78)	0.74
BMI												
Per 5 kg/m^2 increase	1.12 (0.87–1.45)	0.37	1.42 (1.16–1.73)	<0.01	1.04 (0.87–1.23)	0.68	1.91 (1.03–3.53)	0.04	1.21 (0.71–2.05)	0.48	1.06 (0.76–1.47)	0.75
Per 1 SD increase	1.08 (0.91–1.28)		1.26 (1.10–1.44)		1.03 (0.91–1.15)		1.54 (1.02–2.31)		1.14 (0.80–1.61)		1.04 (0.83–1.29)	
SBP												
Per 10 mm Hg increase	1.21 (1.11–1.33)	<0.01	1.20 (1.12–1.30)	<0.01	1.11 (1.03–1.19)	<0.01	1.31 (1.03–1.66)	0.03	0.99 (0.78–1.25)	0.93	1.06 (0.92–1.21)	0.41
Per 1 SD increase	1.33 (1.16–1.51)		1.31 (1.18–1.46)		1.16 (1.05–1.29)		1.49 (1.05–2.11)		0.99 (0.70–1.39)		1.09 (0.89–1.33)	
LDL-C												
Per 1 mmol/L increase	1.77 (1.50–2.09)	<0.01	1.63 (1.41–1.89)	<0.01	1.60 (1.40–1.82)	<0.01	0.51 (0.31–0.85)	0.01	0.63 (0.40–0.98)	0.04	1.08 (0.81–1.45)	0.59
Per 1 SD increase	1.58 (1.38–1.81)		1.48 (1.31–1.67)		1.45 (1.31–1.61)		0.59 (0.39–0.88)		0.69 (0.49–0.98)		1.07 (0.84–1.35)	
HDL-C												
Per 1 mmol/L increase	0.28 (0.17–0.44)	<0.01	0.34 (0.22–0.53)	<0.01	0.36 (0.23–0.55)	<0.01	0.18 (0.05–0.58)	<0.01	0.25 (0.08–0.75)	0.01	0.38 (0.17–0.86)	0.02
Per 1 SD increase	0.61 (0.51–0.73)		0.66 (0.56–0.78)		0.67 (0.57–0.79)		0.51 (0.32–0.81)		0.59 (0.38–0.90)		0.69 (0.50–0.95)	

BMI, body mass index; CAD, coronary artery disease; SBP, systolic blood pressure; HR, hazard ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

of borderline glycemia on subsequent CAD was modest. The combination of CAD+ and diabetes had an additive 15-fold increased risk of future CAD.

Management of CAD risk factors was not sufficient in the CAD− groups regardless of glycemic status and in those with normoglycemia and CAD+. On the other hand, traditional risk factors were well managed in borderline glycemia and diabetes with CAD+. Our results showed that the absolute risks were exclusively high in those with diabetes and CAD+, suggesting that even in Japanese, individuals with diabetes with CAD+ are at high risk for subsequent CAD similar to those in Western countries.

Reports from Western countries showed that in those with diabetes and CAD−, normoglycemia and CAD+, and diabetes with CAD+, risks of a subsequent CAD event were 1.5- to 2.0-fold, 2.0-to 3.0-fold, and 4.0-to 7.0-fold, respectively [3–6]. In our present study, the risk in those with CAD+ was higher compared with those findings. East Asians are less obese and have fewer coronary artery atherosclerotic lesions compared with Westerners [20], suggesting that the risk of CAD is relatively low in both non-diabetic [21,22] and diabetic [23,24] individuals. Nevertheless, in situations wherein there are overlapping risks in those with CAD+, patients with CAD+ had changes in coronary arteries, which greatly increases the risk of subsequent CAD, especially in those with diabetes. Even in East Asians, clinicians must pay attention to populations at high risk of CAD similar to Western populations [3,25–27].

Previous studies showed that CAD increased by 1.2-fold in those with borderline glycemia [11] [12]. Although the influence of borderline glycemia defined by FPG and HbA1c itself was not high compared to diabetes, the incidence of new CAD increased to the same extent as with diabetes in those with other risk factors such as related to blood pressure, lipids, and obesity [13,14]. Thus, in borderline glycemia, especially in those with prior CAD and other metabolic risk factors, active interventions in treating traditional risk factors are required for secondary prevention of CAD [28]. In our present study, traditional risk factors were well controlled compared with previous studies [29] [30]. These risk factors were not independently associated with future CAD and the absolute risk of borderline glycemia with CAD+ was approximately the same as in normoglycemia with CAD+. Those findings were consistent with findings of a recent study that cardiac mortality or the incidence of cardiovascular disease in those with prior CAD does not differ between individuals with borderline glycemia and normoglycemia [31].

Borderline glycemia defined by FPG and HbA1c with CAD+ did not have an additive risk increase unlike diabetes with CAD+; however, those with borderline glycemia had more advanced coronary artery lesions than those with normoglycemia [32–34]. This may be the result of good management of not only traditional risk factors but of residual risk factors such as heart failure, chronic kidney disease, etc. [35] that we could not evaluate in our research. It is possible that the influence of CAD+ differs according to glucose abnormality status.

Haffner et al. [7] revealed that patients with diabetes with CAD− had a risk of CAD as high as that in patients without diabetes with CAD+. Recently, the control status of individual risk factors has improved in real-world settings [36,37]. Bulugahapitiya et al. [2] and Rana et al. [3] showed that diabetes alone did not confer a risk of CAD equivalent to that of individuals with CAD+. However, few studies have evaluated the impact of borderline glycemia separately from normoglycemia. Our findings demonstrated that the impact of borderline glycemia defined by FPG and HbA1c is modest and diabetes alone is not equivalent to the risk of CAD+ in normoglycemia even if the influence of borderline glycemia is eliminated to the greatest extent possible.

In diabetic patients, those with CAD+ are recognized as an exclusively high-risk group for subsequent CAD and risk management is more strictly performed [28,38]. Actually, our real-word data derived from this extensive data base indicated that traditional risk factors were better controlled in those having diabetes with CAD+ than in those with diabetes and CAD−, and no differences in traditional risk factors were observed between those with and without a subsequent CAD event. As a result, the influence of traditional risk factors on subsequent CAD was not shown in the multivariate analysis. However, despite the fact that traditional risk factors were well controlled in those with diabetes and CAD+, unlike borderline glycemia, the additive risk of subsequent CAD increased approximately 15 times compared to normoglycemia and CAD−. In other words, those with diabetes and CAD+ require further management of residual risks [35] along with interventions to treat traditional risk factors. Recently, new evidence was established that specific sodium–glucose cotransporter 2 inhibitors [25] [27] or glucagon-like peptide 1 receptor agonists [26] improve cardiovascular outcomes in high risk patients including patients with prior CAD. Thus, those two glucose-lowering medications should be considered in such high risk groups to prevent future CAD.

Although the incidence of CAD was lower in women than in men, diabetes was more strongly associated with CAD in women compared with men [39]. Unfortunately, we could not evaluate the impact of glucose abnormality and prior CAD on future CAD among women because the incidence of CAD is too low in this population for a meaningful analysis. Further studies are needed to clarify these points with an adequate number of participants.

Our present study's strengths were its large sample size and accurate definition of glucose abnormality status and CAD based on information from health examinations and the claims database that included information on medical practice, thereby allowing all patients to be stratified according to glucose abnormality status and to be identified as to subsequent CAD. However, our study has some limitations. First, we do not have data from oral glucose tolerance tests so that we could not accurately distinguish patients with diet-controlled diabetes from patients with borderline glycemia since both groups would fall under the same definition, which included HbA1c 42–50 mmol/mol and/or FPG 5.6–6.9 mmol/L. Thus, our results could have overestimated the influence of some of the clinical variables in participants with borderline glycemia. Moreover, we could not distinguish between patients with impaired glucose tolerance and impaired fasting glucose. For these reasons, our findings must be interpreted with caution with regard to borderline glycemia. Further studies are needed to clarify the impact of those two borderline glycemia phenotypes on CAD using oral glucose tolerance test data. Second, we could not strictly separate participants who underwent coronary artery bypass grafting (CABG) from those who had a percutaneous coronary intervention (PCI), individuals with a combination of the two procedures, and participants receiving conservative treatment at baseline because we only had claims data for a limited period. Moreover, our questionnaire only included previous CAD. CABG was shown to be superior to PCI for the endpoint of repeat revascularization in diabetes [40]. We also had no data on mortality and heart failure. Therefore, more detailed studies are needed to confirm our findings, taking into consideration baseline CAD patterns, evidence of baseline or subsequent heart failure and mortality. Third, our study participants were limited to men. It was not possible to evaluate the impact of a glucose abnormality status and prior CAD among women because the incidence of CAD is too low in such a population for meaningful analyses of each category. Fourth, it was not possible to identify participants whose glucose abnormality status and traditional risk factors improved or deteriorated during the study period.

5. Conclusion

Control status of traditional risk factors and their impact on subsequent CAD differed in each category. Influence of borderline glycemia defined by FPG and HbA1c was modest when other risk factors were well managed. Current treatment is not sufficient to prevent subsequent CAD, especially in the high-risk group with diabetes and prior CAD. Individualizing treatment strategies are needed to consider each patient's risk factors, such as glucose abnormality status and prior CAD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.153991.

Funding

This work is supported in part by the Japan Society for the Promotion of Science (18K17897).

Author contributions

M.K., K.F. and H.So contributed to the conception and the design of the study and supervised this research. K.F., N.Y. and H.Se contributed to the acquisition of date. M.K., T.O., M.Y., M.H.Y., M.K., Y.M. and T.Y. contributed analysis and interpretation of the data. M.K., and K.F. prepared the figures and wrote and revised the manuscript. All authors contributed to drafting the article or revising it critically for important intellectual content and final approval of the version to be submitted.

Declaration of competing interest

JMDC, Inc. created a nationwide claims-based database for our group without payment. Although members of this organization participated in the preparation of this manuscript, they did not contribute to analysis of data or the conclusions made. Thus, we feel there is no potential conflict of interest relevant to this report.

Acknowledgements

This work is supported in part by JMDC Inc. We appreciate their provision of the database used in this research.

The authors also thank Mami Haga and Natsuko Tada, Niigata University Faculty of Medicine, for excellent secretarial assistance.

References

[1] Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet (London, England). 2015;385:1397–405.
[2] Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabetic medicine: a journal of the British Diabetic Association 2009;26:142–8.
[3] Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. J Gen Intern Med 2016;31:387–93.
[4] Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, Abildstrom SZ, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117:1945–54.
[5] Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet (London, England). 2010;375:2215–22.
[6] Hadaegh F, Fahimfar N, Khalili D, Sheikholeslami F, Azizi F. New and known type 2 diabetes as coronary heart disease equivalent: results from 7.6 year follow up in a Middle East population. Cardiovasc Diabetol 2010;9:84.
[7] Haffner SM, Lehto S, Ronnemaa T, Pyorala 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;339:229–34.
[8] Norhammar A, Lindback J, Ryden L, Wallentin L, Stenestrand U. Improved but still high short- and long-term mortality rates after myocardial infarction in patients with diabetes mellitus: a time-trend report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission. Heart (British Cardiac Society). 2007;93:1577–83.
[9] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–701.
[10] International Diabetes Federation. IDF diabetes atlas - 8th edition, https://diabetesatlas.org/;2017 [accessed 16 October 2018].
[11] Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ 2016;355:i5953.
[12] Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. J Am Coll Cardiol 2010;55:1310–7.
[13] Qiu M, Shen W, Song X, Ju L, Tong W, Wang H, et al. Effects of prediabetes mellitus alone or plus hypertension on subsequent occurrence of cardiovascular disease and diabetes mellitus: longitudinal study. Hypertension (Dallas, Tex: 1979). 2015;65:525–30.
[14] Fujihara K, Matsubayashi Y, Yamamoto M, Osawa T, Ishizawa M, Kaneko M, et al. Impact of body mass index and metabolic phenotypes on coronary artery disease according to glucose tolerance status. Diabetes Metab 2017;43:543–6.
[15] Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. J Epidemiol 2010;20:413–9.
[16] Fujihara K, Igarashi R, Yamamoto M, Ishizawa M, Matsubayasi Y, Matsunaga S, et al. Impact of glucose tolerance status on the development of coronary artery disease among working-age men. Diabetes Metab 2017;43:261–4.
[17] Harada M, Fujihara K, Osawa T, Yamamoto M, Kaneko M, Ishizawa M, et al. Association of treatment-achieved HbA1c with incidence of coronary artery disease and severe eye disease in diabetes patients. Diabetes & metabolism. 2018; pii: S1262–3636(18)30167–8. doi: https://doi.org/10.1016/j.diabet.2018.08.009.
[18] Harada M, Fujihara K, Osawa T, Yamamoto M, Kaneko M, Kitazawa M, et al. Relationship between number of multiple risk factors and coronary artery disease risk with and without diabetes mellitus. The Journal of Clinical Endocrinology and Metabolism. 2019; pii: 5469228. doi: https://doi.org/10.1210/jc.2019-00168.
[19] Osawa T, Fujihara K, Harada M, Yamamoto M, Ishizawa M, Suzuki H, et al. Higher pulse pressure predicts initiation of dialysis in Japanese patients with diabetes. Diabetes Metab Res Rev 2019;35:e3120.
[20] Iso H. Lifestyle and cardiovascular disease in Japan. J Atheroscler Thromb 2011;18:83–8.
[21] Khang YH, Cho SI, Kim HR. Risks for cardiovascular disease, stroke, ischaemic heart disease, and diabetes mellitus associated with the metabolic syndrome using the new harmonised definition: findings from nationally representative longitudinal data from an Asian population. Atherosclerosis 2010;213:579–85.
[22] Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation 2008;118:2702–9.
[23] Ueki K, Sasako T, Okazaki Y, Kato M, Okahata S, Katsuyama H, et al. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial. The Lancet Diabetes & Endocrinology 2017;5:951–64.
[24] Jung CH, Chung JO, Han K, Ko SH, Ko KS, Park JY. Improved trends in cardiovascular complications among subjects with type 2 diabetes in Korea: a nationwide study (2006–2013). Cardiovasc Diabetol 2017;16:1.
[25] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
[26] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.
[27] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
[28] Cubbon R, Kahn M, Kearney MT. Secondary prevention of cardiovascular disease in type 2 diabetes and prediabetes: a cardiologist's perspective. Int J Clin Pract 2008;62:287–99.
[29] Holman RR, Haffner SM, McMurray JJ, Bethel MA, Holzhauer B, Hua TA, et al. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1463–76.
[30] Bress AP, King JB, Kreider KE, Beddhu S, Simmons DL, Cheung AK, et al. Effect of intensive versus standard blood pressure treatment according to baseline prediabetes status: a post hoc analysis of a randomized trial. Diabetes Care 2017;40:1401–8.
[31] Kiviniemi AM, Lepojarvi ES, Tulppo MP, Piira OP, Kentta TV, Perkiomaki JS, et al. Prediabetes and risk for cardiac death among patients with coronary artery disease: the ARTEMIS study. Diabetes Care 2019;42:1319–25.
[32] Ertan C, Ozeke O, Gul M, Aras D, Topaloglu S, Kisacik HL, et al. Association of prediabetes with diffuse coronary narrowing and small-vessel disease. J Cardiol 2014;63:29–34.
[33] Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, et al. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. Circulation 2014;130:1374–82.
[34] Zhang S, Dai J, Jia H, Hu S, Du H, Li N, et al. Non-culprit plaque characteristics in acute coronary syndrome patients with raised hemoglobinA1c: an intravascular optical coherence tomography study. Cardiovasc Diabetol 2018;17:90.
[35] Lin FJ, Tseng WK, Yin WH, Yeh HI, Chen JW, Wu CC. Residual risk factors to predict major adverse cardiovascular events in atherosclerotic cardiovascular disease patients with and without diabetes mellitus. Sci Rep 2017;7:9179.
[36] Yokoyama H, Araki SI, Kawai K, Yamazaki K, Tomonaga O, Shirabe SI, et al. Declining trends of diabetic nephropathy, retinopathy and neuropathy with improving diabetes care indicators in Japanese patients with type 2 and type 1 diabetes (JDDM 46). BMJ Open Diabetes Res Care 2018;6:e000521.
[37] Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. Diabetes Care 2013;36:2271–9.
[38] Bohn B, Schofl C, Zimmer V, Hummel M, Heise N, Siegel E, et al. Achievement of treatment goals for secondary prevention of myocardial infarction or stroke in 29,325 patients with type 2 diabetes: a German/Austrian DPV-multicenter analysis. Cardiovasc Diabetol 2016;15:72.
[39] Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. Bmj 2018;363:k4247.
[40] Xin X, Wang X, Dong X, Fan Y, Shao W, Lu X, et al. Efficacy and safety of drug-eluting stenting compared with bypass grafting in diabetic patients with multivessel and/or left main coronary artery disease. Sci Rep 2019;9:7268.