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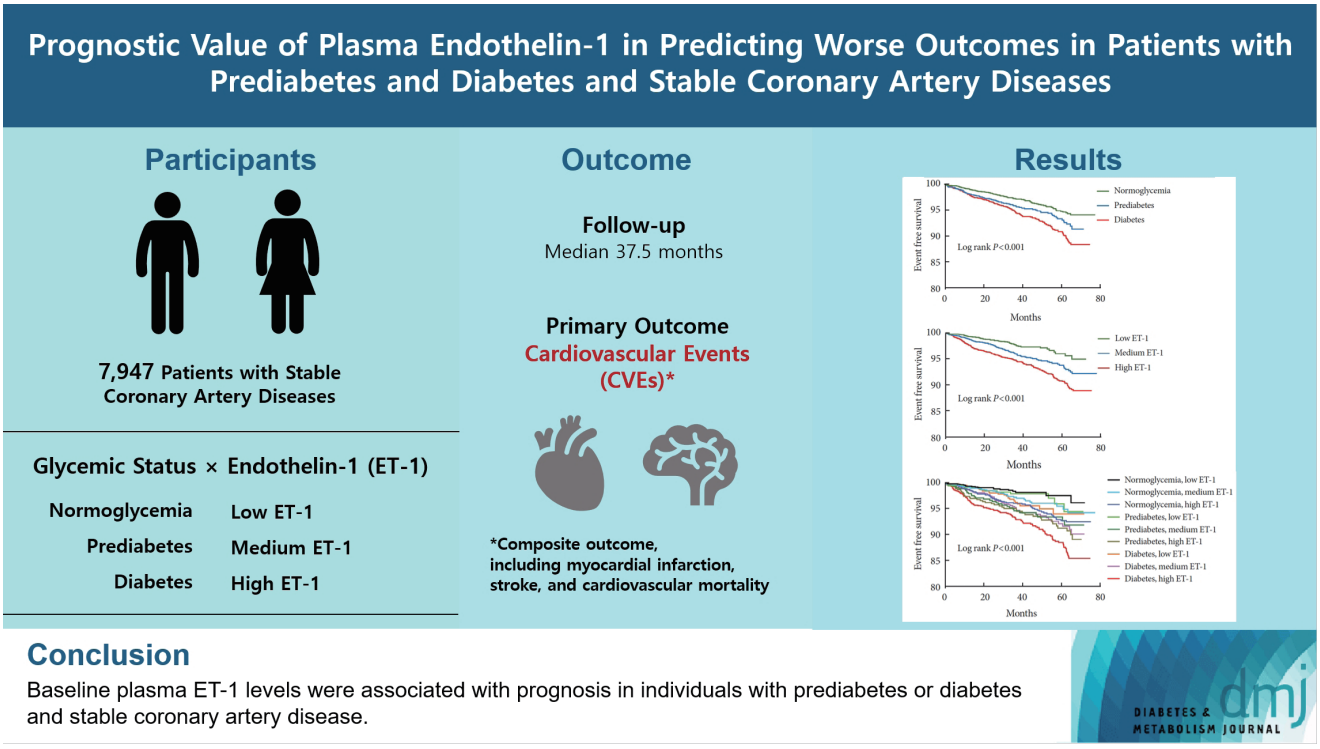

Highlights

- **This study explores ET-1's prognostic value in stable CAD with varied glycemic status.**
- **Elevated ET-1 levels link to higher CVE risk in CAD with prediabetes or diabetes.**
- **Targeting ET-1 pathways may help manage CAD in individuals with dysglycemia.**

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Prognostic Value of Plasma Endothelin-1 in Predicting Worse Outcomes in Patients with Prediabetes and Diabetes and Stable Coronary Artery Diseases

Cheng Yang[1,2], Cheng-Gang Zhu[1], Yuan-Lin Guo[1], Na-Qiong Wu[1], Qian Dong[1], Rui-Xia Xu[1], Yong-Jian Wu[2], Jie Qian[1], Jian-Jun Li[1]

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Background: Endothelin-1 (ET-1) is an endogenous vasoconstrictor implicated in coronary artery disease (CAD) and diabetes. This study aimed to determine the prognostic value of ET-1 in the patients with stable CAD under different glucose metabolism states.
Methods: In this prospective, large-cohort study, we consecutively enrolled 7,947 participants with angiography-diagnosed stable CAD from April 2011 to April 2017. Patients were categorized by baseline glycemic status into three groups (normoglycemia, prediabetes, and diabetes) and further divided into nine groups by circulating ET-1 levels. Patients were followed for the occurrence of cardiovascular events (CVEs), including nonfatal myocardial infarction, stroke, and cardiovascular mortality.
Results: Of the 7,947 subjects, 3,352, 1,653, and 2,942 had normoglycemia, prediabetes, and diabetes, respectively. Over a median follow-up of 37.5 months, 381 (5.1%) CVEs occurred. The risk for CVEs was significantly higher in patients with elevated ET-1 levels after adjustment for potential confounders. When patients were categorized by both status of glucose metabolism and plasma ET-1 levels, the high ET-1 levels were associated with higher risk of CVEs in prediabetes (adjusted hazard ratio [HR], 2.089; 95% confidence interval [CI], 1.151 to 3.793) and diabetes (adjusted HR, 2.729; 95% CI, 1.623 to 4.588; both $P<0.05$).
Conclusion: The present study indicated that baseline plasma ET-1 levels were associated with the prognosis in prediabetic and diabetic patients with stable CAD, suggesting that ET-1 may be a valuable predictor in CAD patients with impaired glucose metabolism.

Keywords: Coronary artery disease; Diabetes mellitus; Endothelin-1; Prediabetic state; Prognosis

INTRODUCTION

Coronary artery disease (CAD) is one of the major cardiovascular diseases threatening adults worldwide [1,2]. Patients with diabetes mellitus are at increased risk of cardiovascular events (CVEs) [3]. Despite advancements in medical and interventional therapies, cardiovascular morbidity and mortality rates remain high, especially in patients with comorbid diabetes [4]. Diabetes is not only a major risk factor for the development of CAD but is also associated with adverse clinical outcomes

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[5,6]. Prediabetes, an intermediate stage of glucose dysregulation that may precede type 2 diabetes mellitus, affected approximately 720 million individuals worldwide in 2021 and is projected to impact 1 billion individuals by 2045 [7-9]. Emerging evidence has demonstrated that prediabetes is associated with a higher risk of mortality and cardiovascular disease in both the general population and in patients with atherosclerotic cardiovascular disease [10,11].

Endothelin-1 (ET-1), an endothelium-derived peptide, is the most potent endogenous vasoconstrictor [12] and contributes to basal vascular tone as well as a number of diseases, such as atherosclerosis, ischemic heart disease, hypertension, pulmonary arterial hypertension, chronic kidney disease, and congestive heart failure [13-16]. Previous studies have shown that plasma ET-1 level is a risk factor of CVEs in patients with stable CAD [17-19]. However, no studies have investigated the potential role of the plasma ET-1 concentrations in predicting adverse clinical outcomes in patients with stable CAD, based on the glucose metabolism status.

On the basis of the above, we performed a prospective analysis in a cohort of patients with stable CAD who underwent elective coronary angiography. Our aim was to investigate potential correlations between plasma ET-1 level and prospective CVEs in three groups with normoglycemia, prediabetes, and diabetes.

METHODS

Study design and participants

This study was in accordance with the principles set by the Declaration of Helsinki and was approved by the Ethics Review Board of Fuwai Hospital (IRB No. 2013-442). Informed written consents were obtained from all participants enrolled in this study.

The details were described in the flowchart (Fig. 1), from April 2011 to April 2017, 8,986 consecutive participants from 20 provinces in China were admitted in Fuwai Hospital and

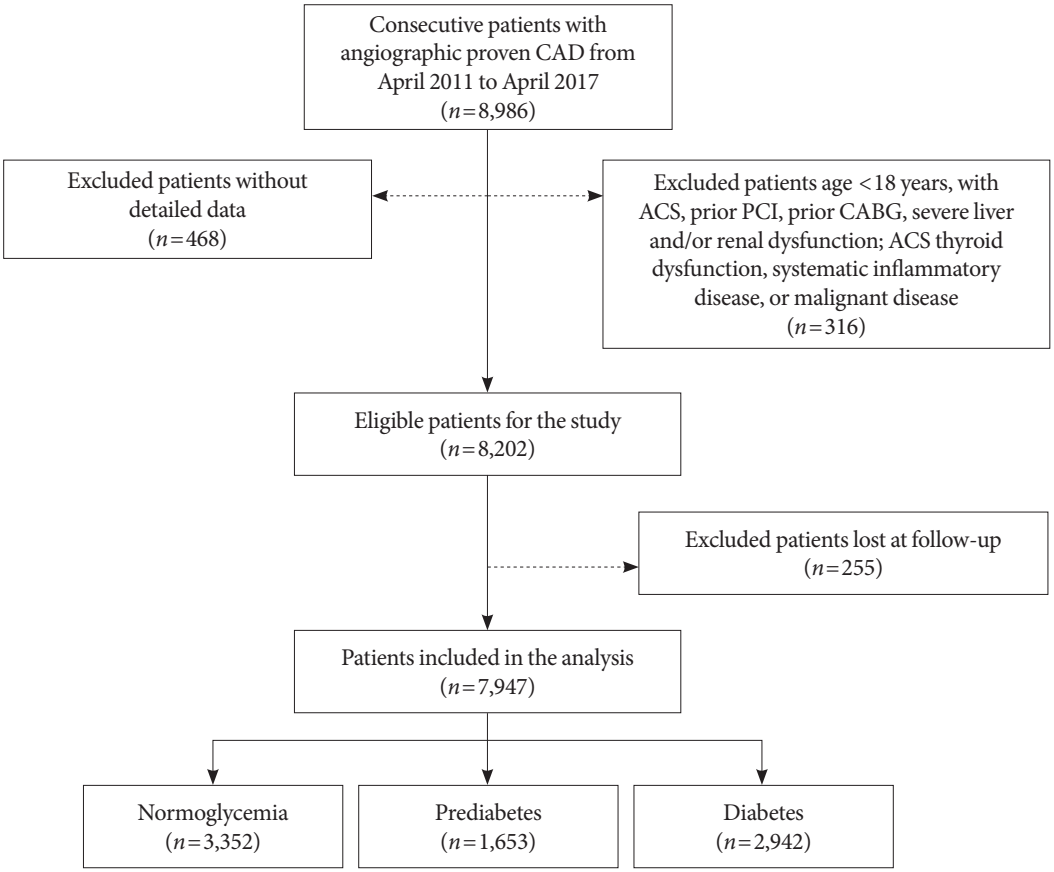

Fig. 1. Study flow chart. CAD, coronary artery disease; ACS, acute coronary syndrome; PCI, percutaneous coronary artery intervention; CABG, coronary artery bypass grafting.

scheduled for coronary angiography due to angina-like chest pain and/or positive treadmill exercise test or clinically suspected CAD. The exclusion criteria included missing detailed data, age <18 years, acute coronary syndrome, previous percutaneous coronary artery intervention, and coronary artery bypass grafting, severe liver and/or renal insufficiency, thyroid dysfunction, systematic inflammatory disease, and malignant disease. Finally, a total of 7,947 participants were included and categorized by baseline glycemic status into three groups: normoglycemia, prediabetes, and diabetes.

Definition of clinical status

CAD was defined as the presence of coronary stenosis ≥ 50% at least one major artery segment assessed by two experienced physicians, according to coronary angiography. Baseline glycemic status was defined according to World Health Organization (WHO)/International Expert Committee (IEC) criteria [20]. Diabetes was diagnosed as fasting plasma glucose (FPG) ≥7.0 mmol/L, glycosylated hemoglobin (HbA1c) level ≥6.5%, or current use of hypoglycemic drugs or insulin. Prediabetes was diagnosed in participants who had no self-reported diabetes or hypoglycemic therapies but had a FPG ranging from 6.1 to 6.9 mmol/L, or HbA1c level ranging from 6.0% to 6.4%. Patients who were without diabetes or prediabetes were defined as normoglycemia. Hypertension was defined as self-reported hypertension, currently taking antihypertensive drugs, or recorded systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg three or more consecutive times. Information regarding other disease, family history, and prior therapy of each participant was collected from self-reported or hospital-recorded medical history.

Laboratory methods

Blood samples were collected from each patient after fasting for at least 12 hours before coronary angiography. The concentrations of plasma glucose were measured by enzymatic hexokinase method. HbA1c was evaluated using Tosoh Automated Glycohemoglobin Analyser (HLC-723G8, Tosoh, Tokyo, Japan). Circulating plasma ET-1 levels were measured using a highly sensitive and specific commercial sandwich enzyme immunoassay (BI-20082H, Biomedica, Wien, Austria). The normal range was less than 0.25 pmol/L, and the detection sensitivity was 0.02 pmol/L. Intra-assay coefficient of variation (10 replicates) was 4%, and inter-assay precision (five assay runs) was 5%. Concentrations of lipid parameters, including triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and lipoprotein(a) (Lp(a)) were measured using automatic biochemistry analyzer (Hitachi 7150, Hitachi, Tokyo, Japan) in an enzymatic assay. Concentrations of fibrinogen were measured using a Stago auto analyzer by the Clauss method with an STA Fibrinogen kit (Diagnostica Stago, Taverny, France). Plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP) was determined using an electrochemiluminescence immunoassay (ECLIA) method (Roche Diagnostics, Mannheim, Germany) with a Roche modular analytics E170 immunoassay analyzer.

Clinical outcomes and follow-up

The primary outcome of this study was CVEs, which is the composite of cardiovascular death, stroke, nonfatal myocardial infarction. Nonfatal myocardial infraction was defined as the presence of positive cardiac troponins accompanied by typical chest pain, typical electrocardiogram serial changes, identification of an intracoronary thrombus by angiography or autopsy, or imaging evidence of new loss of viable myocardium or a new regional wall-motion abnormality. Stroke was identified using detailed medical records and cranial imaging. Patients were followed up every 6 months. Trained doctors or nurses, blinded to the clinical and laboratory data, collected the data from medical records, clinical visit, and/or telephone interviews in accordance with standard protocols. They completed detailed case report forms for each event, providing sufficient information for independent medical assessment. Three qualified physicians independently adjudicated events based on predefined criteria and centralized review. If disagreements arose, events were reassessed, and final outcomes were determined by consensus.

Statistical analysis

Baseline characteristics were presented as mean±standard deviation (SD) or median (interquartile range) for continuous variables and as a frequency (percentage) for categorical variables. Differences were assessed for statistical significance using a Wilcoxon rank sum test, a Kruskal-Wallis test or an analysis of variance (ANOVA) for continuous data and chi-square test (or Fisher exact test where the expected cell value was <5) for categorical variables. The event-free survival rates among groups were the Kaplan-Meier method and compared by the log-rank test. The associations among ET-1, glycemic status, and clinical outcomes were analyzed by the unadjusted and

adjusted Cox regression analyses (showed with hazard ratios [HR] and 95% confidence intervals [CI]). Confounders included age, sex, body mass index (BMI), current smoking, hypertension, peripheral artery disease, family history of CAD, left ventricular ejection fraction, NT-proBNP, TG, LDL-C, HDL-C, Lp(a), fibrinogen, diseased vessels, and baseline statins, aspirin, angiotensin II receptor blockers, β-blockers, and calcium channel blockers treatments. Multivariable-adjusted HRs with corresponding 95% CI were calculated for the overall cohort and for ET-1 levels and glycemic status.

Two-sided *P* values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software version 22.0 (IBM Co., Armonk, NY, USA) and R language 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

The baseline characteristics of 7,947 participants (mean age, 57.48±10.49 years; men, 72.6%) are shown in Table 1. Among them, 3,352 (42.2%), 1,653 (20.8%), and 2,942 (37.0%) were diagnosed as normoglycemia, prediabetes, and diabetes, respectively. There was no significant difference regarding family history of CAD, TC, serum creatinine, and proportion of angiotensin-converting enzyme inhibitors treatments among the three groups ($P>0.05$). The BMI, FPG, HbA1c, TG, and ET-1 were positively associated with baseline glycemic states from normoglycemia to diabetes (all $P<0.05$). Supplymentary Fig. 1 displays the distribution of plasma ET-1 levels among overall participants and different glycemic status groups.

Association between ET-1 levels and adverse clinical outcomes

Over a median follow-up time of 37.5 months (23.2 to 55.3), 381 CVEs occurred (121 died, 92 suffered nonfatal MI, and 168 had nonfatal strokes). According to tertiles of plasma ET-1 levels, ET-1 was divided into three groups: low ET-1 (ET-1 <0.20 pmol/L), medium ET-1 (0.20≤ ET-1 <0.29 pmol/L), and high ET-1 (ET-1 >0.29 pmol/L). Univariate Cox proportional hazard regression analysis demonstrated that patients with high ET-1 levels had a 2.509-fold increased risk of CVEs (HR, 2.509; 95% CI, 1.870 to 3.366; $P<0.001$) (Table 2). In multivariate Cox proportional hazard regression analysis, plasma ET-1 levels were also associated with CVEs (medium ET-1: adjusted HR, 1.465; 95% CI, 1.051 to 2.043; $P=0.024$; high ET-1: adjusted HR, 1.750; 95% CI, 1.272 to 2.406; $P=0.001$) (Table 2). The Cox prediction models of plasma ET-1 levels for CVEs yielded C-statistic values of 0.694 (95% CI, 0.664 to 0.722; $P<0.001$).

Glucose metabolism, ET-1 levels, and cardiovascular outcomes

The prevalence of CVEs in normoglycemia, prediabetes, and diabetes groups with stable CAD was 3.3%, 5.0%, and 6.5%, respectively (Fig. 2). Kaplan-Meier analysis showed that diabetes subjects had the lowest event-free survival rate among the three groups (log-rank $P<0.001$) (Fig. 3A). Multivariate Cox regression models showed that patients with diabetes had 1.511-fold higher risk of CVEs than normoglycemia subjects (HR, 1.511; 95% CI, 1.177 to 1.939; $P=0.001$), while the patients with prediabetes had no significant higher risk of CVEs than normoglycemia subjects (adjusted HR, 1.209; 95% CI, 0.899 to 1.624; $P=0.209$).

Kaplan-Meier analysis showed that patients with high ET-1 levels had the lowest event-free survival rate among the three groups (Fig. 3B). However, when the patients were evaluated according to both glucose metabolism status and circulating ET-1 concentrations, those patients with diabetes plus high ET-1 levels had a significantly higher risk of CVEs than the reference group (normoglycemia plus low ET-1 levels, $P<0.001$) (Fig. 3C). Multivariate Cox regression analyses according to both glucose metabolism status and ET-1 status indicated that patients in diabetes plus high ET-1, diabetes plus medium ET-1, prediabetes plus high ET-1 groups had 2.661-fold (95% CI, 1.582 to 4.476), 1.932-fold (95% CI, 1.113 to 3.352), and 1.910-fold (95% CI, 1.069 to 3.413) higher risk of CVEs (all $P<0.05$, respectively) (Table 3).

DISCUSSION

In this prospective study, we, for the first time, investigated the association of circulating ET-1 on CVEs in stable, angiography-proven CAD patients with different glucose metabolism status. There are several major findings in our study. First, we confirmed that baseline plasma ET-1 level is an independent predictor of CVEs in patients with stable CAD. Secondly, ET-1 remains independently associated with worse cardiovascular outcomes in prediabetic and diabetic patients but not in patients with normoglycemia when multivariate Cox propor-

Table 1. Baseline characteristics of the study population

Variable	Overall	Baseline glycemic status			*P* value
		Normoglycemia	Prediabetes	Diabetes	
Number	7,947	3,352	1,653	2,942	
Age, yr	57.48±10.49	55.39±10.80	59.21±9.54	58.88±10.23	<0.001
Male sex	5,771 (72.6)	2,549 (76.0)	1,146 (69.3)	2,076 (70.6)	<0.001
BMI, kg/m^2	25.92±3.18	25.49±3.13	25.98±3.24	26.37±3.14	<0.001
Medical history					
Hypertension	4,971 (62.6)	1,878 (56.0)	1,017 (61.5)	2,076 (70.6)	<0.001
Dyslipidemia	6,035 (75.9)	2,404 (71.7)	1,256 (76.0)	2,375 (80.7)	<0.001
Type 2 diabetes mellitus	2,234 (28.1)	0	0	2,234 (75.9)	<0.001
Stroke	245 (3.08)	89 (2.66)	55 (3.33)	101 (3.43)	0.166
Peripheral artery disease	99 (1.25)	24 (0.72)	26 (1.57)	49 (1.67)	0.001
Current smoking	4,388 (55.2)	1,920 (57.3)	872 (52.8)	1,596 (54.2)	0.004
Family history of coronary artery disease	1,106 (13.9)	497 (14.8)	215 (13.0)	394 (13.4)	0.126
Laboratory data					
Endothelin-1, pmol/L	0.23 (0.18–0.33)	0.22 (0.17–0.32)	0.23 (0.17–0.33)	0.25 (0.19–0.35)	<0.001
FPG, mmol/L	5.87±1.78	4.95±0.52	5.37±0.68	7.19±2.28	<0.001
HbA1c, %	6.33±1.11	5.56±0.29	6.11±0.22	7.34±1.23	<0.001
Triglyceride, mmol/L	1.50 (1.10–2.09)	1.44 (1.05–2.00)	1.52 (1.12–2.07)	1.57 (1.17–2.20)	0.006
Total cholesterol, mmol/L	4.12±1.16	4.12±1.15	4.16±1.18	4.09±1.18	0.175
LDL-C, mmol/L	2.49±0.98	2.51±1.01	2.52±0.92	2.45±0.96	0.011
HDL-C, mmol/L	1.05±0.29	1.06±0.30	1.07±0.28	1.03±0.28	<0.001
Lipoprotein (a), mg/dL	15.09 (6.70–36.57)	15.52 (6.91–37.84)	15.88 (7.08–38.55)	14.23 (6.37–34.16)	0.002
Apolipoprotein A1, g/L	1.33±0.29	1.32±0.28	1.36±0.27	1.33±0.31	0.001
Apolipoprotein B, g/L	0.91±0.29	0.91±0.29	0.90±0.28	0.92±0.30	0.479
Fibrinogen, g/L	3.21±0.82	3.09±0.73	3.28±0.96	3.32±0.80	<0.001
Serum creatinine, mmol/L	77.42±15.75	77.63±14.93	76.80±14.62	77.52±17.22	0.195
Left main ejection fraction, %	63.77±7.43	64.06±7.32	63.88±7.44	63.36±7.54	0.001
NT-proBNP, fmol/mL	334.4 (60.5–571.4)	224.0 (51.2–527.1)	393.1 (83.9–612.1)	373.6 (69.0–598.7)	<0.001
Baseline medications					
Statins	7,200 (90.6)	2,972 (88.7)	1,538 (93.0)	2,690 (91.4)	<0.001
Aspirin	7,515 (94.6)	3,112 (92.8)	1,595 (96.5)	2,808 (95.4)	0.003
Angiotensin-converting enzyme inhibitors	1,904 (24.0)	769 (22.9)	411 (24.9)	724 (24.6)	0.189
Angiotensin II receptor blockers	1,924 (24.2)	698 (20.8)	389 (23.5)	837 (28.5)	<0.001
β-Blockers	6,104 (76.8)	2,466 (73.6)	1,277 (77.3)	2,361 (80.3)	<0.001
Calcium channel blockers	2,999 (37.7)	1,132 (42.2)	669 (40.5)	1,198 (40.7)	<0.001
Diseased vessels					<0.001
One vessel	3,513 (44.21)	1,652 (49.30)	729 (44.10)	1,132 (38.48)	
Two vessels	2,082 (26.20)	860 (25.66)	432 (26.13)	790 (26.85)	
Three vessels	2,352 (29.60)	840 (25.06)	492 (29.76)	1,020 (34.67)	
Revascularization strategies					
PCI	3,195 (40.20)	1,321 (39.41)	662 (40.05)	1,212 (41.20)	0.350
CABG	80 (1.01)	33 (0.98)	17 (1.03)	30 (1.02)	0.985

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PCI, percutaneous coronary artery intervention; CABG, coronary artery bypass grafting.

Table 2. Association of ET-1 with composite and separate cardiovascular events

Variable	Events/Subject	HR (95% CI)	
		Crude model	Adjusted model
Composite cardiovascular events			
Low ET-1	58/2,628	Reference	Reference
Medium ET-1	115/2,565	1.743 (1.270–2.391)[a]	1.465 (1.051–2.043)[a]
High ET-1	208/2,754	2.509 (1.870–3.366)[a]	1.750 (1.272–2.406)[a]
Nonfatal myocardial infarction			
Low ET-1	9/2,628	Reference	Reference
Medium ET-1	30/2,565	3.038 (1.441–6.403)[a]	3.167 (1.432–7.002)[a]
High ET-1	58/2,754	4.848 (2.393–9.820)[a]	4.501 (2.090–9.692)[a]
Stroke			
Low ET-1	39/2,628	Reference	Reference
Medium ET-1	49/2,565	1.062 (0.696–1.619)	0.977 (0.625–1.528)
High ET-1	75/2,754	1.242 (0.838–1.840)	0.997 (0.646–1.539)
Cardiovascular death			
Low ET-1	10/2,628	Reference	Reference
Medium ET-1	36/2,565	3.222 (1.598–6.497)[a]	2.077 (1.016–4.244)[a]
High ET-1	75/2,754	5.463 (2.815–10.600)[a]	2.493 (1.255–4.953)[a]

Univariate and multivariate Cox proportional hazards regression analysis was performed in crude and adjusted models respectively. Model adjusted for age, sex, body mass index, current smoking, hypertension, peripheral artery disease, family history of coronary artery disease, left ventricular ejection fraction, glycosylated hemoglobin, N-terminal pro–B-type natriuretic peptide, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipoprotein(a), fibrinogen, diseased vessels, and baseline statins, aspirin, angiotensin II receptor blockers, β-blockers, and calcium channel blockers treatments.
ET-1, endothelin-1; HR, hazard ratio; CI, confidence interval.
[a]$P<0.05$.

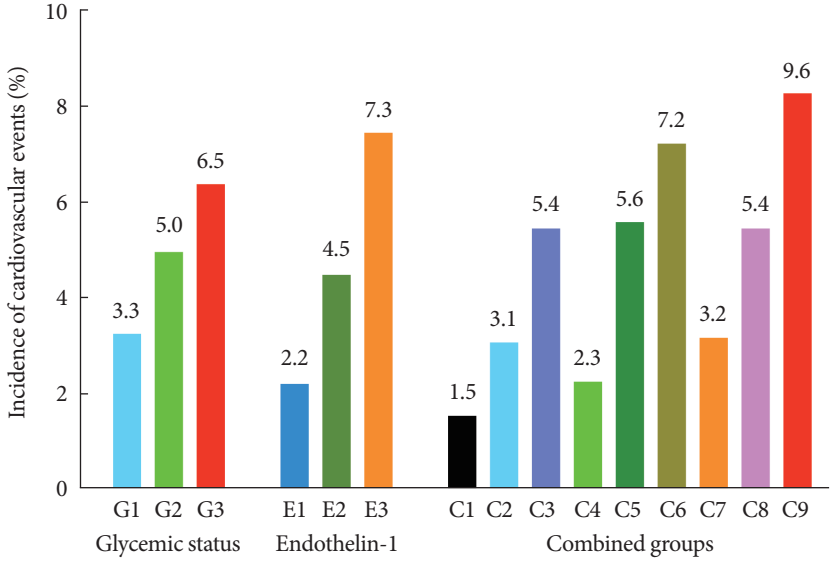

Fig. 2. The incident rates of cardiovascular events in different glucose metabolism status, endothelin-1 (ET-1) levels and status of both ET-1 levels and glycemic status. G1, normoglycemia; G2, prediabetes; G3, diabetes; E1, low ET-1 levels; E2, medium ET-1 levels; E3, high ET-1 levels; C1, normoglycemia+low ET-1 levels; C2, normoglycemia+medium ET-1 levels; C3, normoglycemia+high ET-1 levels; C4, prediabetes+low ET-1 levels; C5, prediabetes+medium ET-1 levels; C6, prediabetes+high ET-1 levels; C7, diabetes+low ET-1 levels; C8, diabetes+medium ET-1 levels; C9, diabetes+high ET-1 levels.

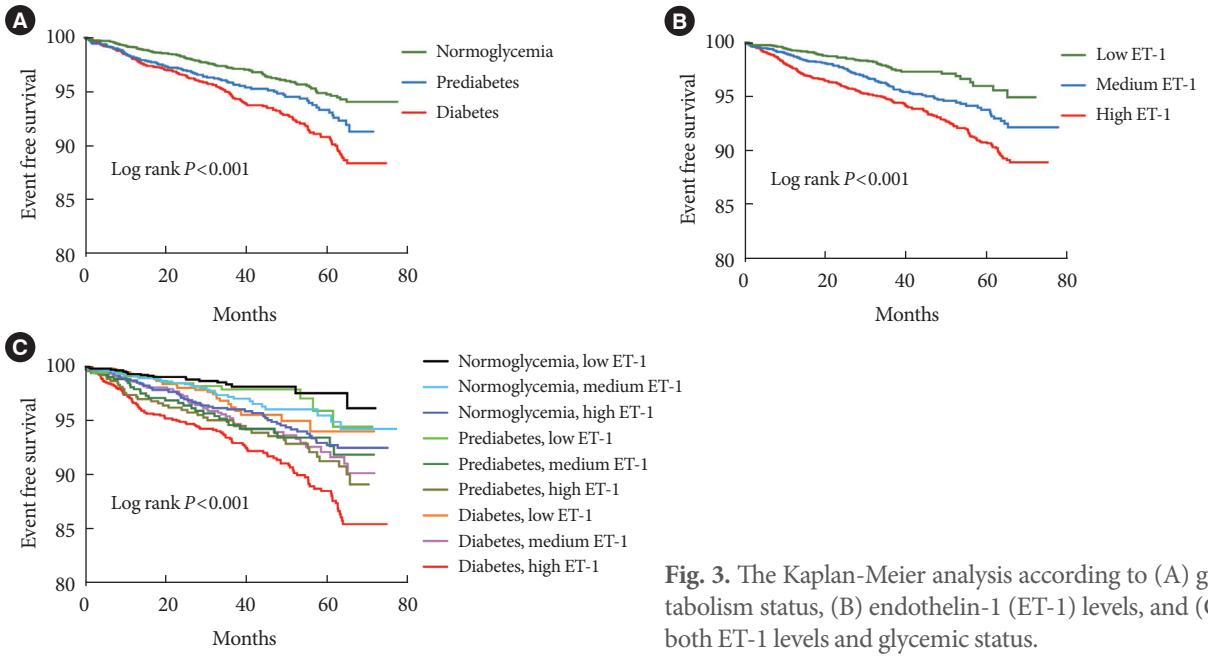

Fig. 3. The Kaplan-Meier analysis according to (A) glucose metabolism status, (B) endothelin-1 (ET-1) levels, and (C) status of both ET-1 levels and glycemic status.

Table 3. Association of ET-1 levels with cardiovascular events in patients with different glucose metabolism status

ET-1	Events/Subject	HR (95% CI)	
		Crude model	Adjusted model
Normoglycemia			
Low ET-1	19/1,232	Reference	Reference
Medium ET-1	33/1,073	1.724 (0.980–3.033)	1.415 (0.790–2.534)
High ET-1	57/1,047	2.450 (1.455–4.126)[a]	1.695 (0.983–2.922)
Prediabetes			
Low ET-1	13/576	1.379 (0.681–2.792)	1.099 (0.536–2.250)
Medium ET-1	30/537	2.920 (1.642–5.192)[a]	2.091 (1.152–3.796)[a]
High ET-1	39/540	3.318 (1.913–5.753)[a]	1.910 (1.069–3.413)[a]
Diabetes			
Low ET-1	26/820	2.007 (1.111–3.626)	1.497 (0.803–2.791)
Medium ET-1	52/955	2.941 (1.738–4.977)[a]	1.932 (1.113–3.352)[a]
High ET-1	112/1,157	4.640 (2.848–7.559)[a]	2.661 (1.582–4.476)[a]

Univariate and multivariate Cox proportional hazards regression analysis was performed in crude and adjusted models respectively. Model adjusted for age, sex, body mass index, current smoking, hypertension, peripheral artery disease, family history of coronary artery disease, left ventricular ejection fraction, N-terminal pro–B-type natriuretic peptide, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipoprotein(a), fibrinogen, diseased vessels, and baseline statins, aspirin, angiotensin II receptor blockers, β-blockers, and calcium channel blockers treatments.
ET-1, endothelin-1; HR, hazard ratio; CI, confidence interval.
[a]$P<0.05$.

tional hazards analysis is performed. Finally, patients with diabetes and high ET-1 levels were associated with the highest risk of CVEs in patients with stable CAD. Thus, our study firstly suggested the joint predictive value of glycemic status and ET-1 levels on CVEs in patients with stable CAD.

ET-1 is a 21 amino acid neurohormone that acts as a highly potent endogenous vasoconstrictor that was first discovered from aortic endothelial cell culture media in 1988 [12]. Locat-

ed on chromosome 6, ET-1 production and secretion are primarily controlled at the gene transcriptional level and are produced by vascular endothelial and smooth muscle cells, pancreatic islets, airway epithelial cells, macrophages, fibroblasts, cardiac myocytes, and brain neurons. The production of ET-1 is upregulated by thrombin, insulin, cyclosporine, epinephrine, angiotensin II, cortisol, inflammatory mediators, hypoxia, and vascular shear stress [21]. Secreted ET-1 activates endothelin receptors type-A and type-B (both G-protein-coupled receptors) on vascular smooth muscle resulting in increased intracellular calcium and vasoconstriction [22,23]. Serum levels of ET-1 are pathologically elevated in a host of different diseases, including cardiovascular diseases [24]. Not surprisingly, the endothelin system has become a target for therapeutic interventions, with a few already established agents. For instance, endothelin receptor antagonists have been developed an important treatment for primary pulmonary hypertension [25].

Cardiovascular diseases such as CAD are major contributors to the global burden of disease and the socioeconomic health costs [26,27]. ET-1 has been implicated in the pathogenesis of atherosclerosis, contributing to myocardial ischemia and hypoxia through microvascular dysfunction induced by excessive vasoconstriction [28]. Several studies have also demonstrated the predictive value of ET-1 in patients with established CAD. In a prospective study, 3,154 patients with stable CAD were enrolled and followed up for 2 years. The results showed that high ET-1 levels were positively correlated with a combined endpoint of death or CVEs including stroke, nonfatal myocardial infarction, and revascularization (HR, 1.656; 95% CI, 1.099 to 2.496; P=0.016) [18]. In consistent with this finding, a sub-analysis of the Prevention of Events with Angiotensin Converting Enzyme (PEACE) trial, which investigated 3,717 patients with stable CAD, indicated that higher C-terminal proET-1 level (per SD increase or 4th quartile level) was significantly associated with the combined endpoint of cardiovascular death or heart failure hospitalization [17]. Concordant with those observations, in our dataset aimed at providing further evidence of the therapeutic and predictive value of this crucial marker in stable CAD patients, we investigated the association of plasma ET-1 to CVEs in a larger population with longer follow-up periods, particularly in patients with abnormal glucose metabolism.

Abnormal glucose regulation, including prediabetes and diabetes, is a well-established risk factor for CAD [29,30]. Prediabetes, an intermediate stage between normoglycemia and diabetes, is prone to poor management. Individuals with prediabetes, identified by impaired fasting glucose, impaired glucose tolerance, or both, exhibit varying degrees of insulin resistance and beta cell dysfunction, with near-maximal insulin resistance [31,32]. Compared with individuals with normal glucose regulation, those with prediabetes who have more cardiovascular disease risk factors and an increased incidence of CVEs. A meta-analysis, involving 10,069,955 individuals from 129 prospective studies with a median follow-up of 9.8 years revealed that prediabetes at baseline was associated with increased rates of cardiovascular disease (incidence rate per 10,000 person-years, 58.3 in those with normal glucose regulation vs. 67.0 among those with prediabetes) and all-cause mortality (incidence rate per 10,000 person-years, 73.6 in those with normal glucose regulation vs. 81 among those with prediabetes) [11]. Furthermore, diabetes is a unique clinical setting characterized by exceedingly high rates of morbidity and mortality. Indeed, cardiovascular disease accounts for approximately half of all deaths among patients with diabetes [33]. In view of the above, CAD patients with abnormal glucose regulation should be examined more closely valuable prognostic biomarker. Early studies have revealed that ET-1 contributed to endothelial dysfunction and the dysregulation of glucose metabolism observed both in subjects with insulin resistance and patients with diabetes [34]. Moreover, elevated ET-1 may have an effect on diabetic cardiovascular complications due to its proliferative, profibrotic, and proinflammatory properties [14,35]. However, no study on the combined effect of high ET-1 levels and glucose metabolic states on risk of CVEs in patients with stable CAD is currently available. In the present study, we not only focused on the prognosis of ET-1 levels in patients with stable CAD, but also paid attention to the joint effect of elevated plasma ET-1 levels and prediabetes or diabetes on cardiovascular outcomes. As the main novel findings of our study, patients with prediabetes and high ET-1 levels or diabetes and high ET-1 levels had 1.910- and 2.661-fold higher risk of CVEs, respectively.

Taken together, our findings demonstrate that plasma ET-1 is a prognosticator for worse cardiovascular outcomes in CAD patients under different glycemic states, particularly, prediabetic and diabetic patients with high ET-1 levels had a worse prognosis.

Our analysis has several limitations that should be considered. First, this is an observational study, susceptible to unidentified biases inherent in such analysis, despite multivariable adjustment to control for common potential confounding

variables. Secondly, the patients who consented and enrolled in the present study are from a single, large cardiovascular disease center in China; as a result, the findings may not be generalizable to the other ethnicities. Thirdly, only baseline plasma ET-1 levels are available in this dataset, and therefore may not provide insights into dynamic changes in circulating ET-1 concentrations with treatment. Finally, the underlying mechanism of this association warrants further investigation.

In conclusion, the current study indicated an independent association between elevated ET-1 levels and cardiovascular outcomes in patients with stable CAD. Moreover, ET-1 provides significant prognostic information in stable CAD patients that enhances information provided by glycemic status. Patients with diabetes and high ET-1 levels were found to have the highest risk of CVEs, suggesting that the measurement of ET-1 concentrations and potential treating strategies toward ET-1 might be beneficial in CAD patients with prediabetes and diabetes.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2023.0410.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: C.Y., J.Q., J.J.L.
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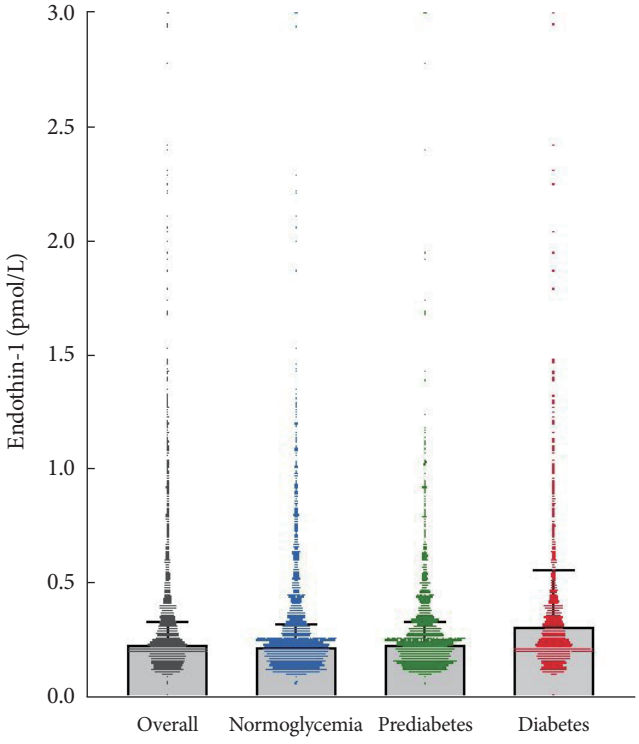
REFERENCES

1. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1223-49.
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. J Am Coll Cardiol 2020;76:2982-3021.
3. Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2015;132:691-718.
4. Kelsey MD, Nelson AJ, Green JB, Granger CB, Peterson ED, McGuire DK, et al. Guidelines for cardiovascular risk reduction in patients with type 2 diabetes: JACC guideline comparison. J Am Coll Cardiol 2022;79:1849-57.
5. Liu Y, Yang YM, Zhu J, Tan HQ, Liang Y, Li JD. Prognostic significance of hemoglobin A1c level in patients hospitalized with coronary artery disease: a systematic review and meta-analysis. Cardiovasc Diabetol 2011;10:98.
6. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J 2013;34:2436-43.
7. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. Lancet 2012;379:2279-90.
8. Echouffo-Tcheugui JB, Perreault L, Ji L, Dagogo-Jack S. Diagnosis and management of prediabetes: a review. JAMA 2023;329:1206-16.
9. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119.
10. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between pre-

diabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ 2016;355:i5953.
11. Cai X, Zhang Y, Li M, Wu JH, Mai L, Li J, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. BMJ 2020;370:m2297.
12. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988;332:411-5.
13. Schooling CM, Kodali H, Li S, Borrell LN. ET (endothelin)-1 and ischemic heart disease: a mendelian randomization study. Circ Genom Precis Med 2018;11:e002026.
14. Ergul A. Endothelin-1 and diabetic complications: focus on the vasculature. Pharmacol Res 2011;63:477-82.
15. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. Kidney Int 2014;86:896-904.
16. Perez AL, Grodin JL, Wu Y, Hernandez AF, Butler J, Metra M, et al. Increased mortality with elevated plasma endothelin-1 in acute heart failure: an ASCEND-HF biomarker substudy. Eur J Heart Fail 2016;18:290-7.
17. Sabatine MS, Morrow DA, de Lemos JA, Omland T, Sloan S, Jarolim P, et al. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. Circulation 2012;125:233-40.
18. Zhou BY, Guo YL, Wu NQ, Zhu CG, Gao Y, Qing P, et al. Plasma big endothelin-1 levels at admission and future cardiovascular outcomes: a cohort study in patients with stable coronary artery disease. Int J Cardiol 2017;230:76-9.
19. Schnabel RB, Schulz A, Messow CM, Lubos E, Wild PS, Zeller T, et al. Multiple marker approach to risk stratification in patients with stable coronary artery disease. Eur Heart J 2010;31:3024-31.
20. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(Suppl 1):S62-9.
21. Kawanabe Y, Nauli SM. Endothelin. Cell Mol Life Sci 2011;68:195-203.
22. Dhaun N, Webb DJ. Endothelins in cardiovascular biology and therapeutics. Nat Rev Cardiol 2019;16:491-502.
23. Sakurai T, Yanagisawa M, Takuwa Y, Miyazaki H, Kimura S, Goto K, et al. Cloning of a cDNA encoding a non-isopeptide-selective subtype of the endothelin receptor. Nature 1990;348:732-5.
24. Jain A. Endothelin-1-induced endoplasmic reticulum stress in disease. J Pharmacol Exp Ther 2013;346:163-72.
25. Eroglu E, Kocyigit I, Lindholm B. The endothelin system as target for therapeutic interventions in cardiovascular and renal disease. Clin Chim Acta 2020;506:92-106.
26. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-88.
27. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: a compass for future health. J Am Coll Cardiol 2022;80:2361-71.
28. Barton M, Yanagisawa M. Endothelin: 30 years from discovery to therapy. Hypertension 2019;74:1232-65.
29. Hu DY, Pan CY, Yu JM; China Heart Survey Group. The relationship between coronary artery disease and abnormal glucose regulation in China: the China Heart Survey. Eur Heart J 2006;27:2573-9.
30. Ding D, Qiu J, Li X, Li D, Xia M, Li Z, et al. Hyperglycemia and mortality among patients with coronary artery disease. Diabetes Care 2014;37:546-54.
31. Færch K, Johansen NB, Witte DR, Lauritzen T, Jorgensen ME, Vistisen D. Relationship between insulin resistance and β-cell dysfunction in subphenotypes of prediabetes and type 2 diabetes. J Clin Endocrinol Metab 2015;100:707-16.
32. Lorenzo C, Wagenknecht LE, Hanley AJ, Rewers MJ, Karter AJ, Haffner SM. A1C between 5.7 and 6.4% as a marker for identifying pre-diabetes, insulin sensitivity and secretion, and cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study (IRAS). Diabetes Care 2010;33:2104-9.
33. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol 2018;17:83.
34. Schneider JG, Tilly N, Hierl T, Sommer U, Hamann A, Dugi K, et al. Elevated plasma endothelin-1 levels in diabetes mellitus. Am J Hypertens 2002;15:967-72.
35. Matsumoto T, Ozawa Y, Taguchi K, Kobayashi T, Kamata K. Diabetes-associated changes and role of N epsilon-(carboxymethyl)lysine in big ET-1-induced coronary vasoconstriction. Peptides 2010;31:346-53.



Supplementary Fig. 1. The distribution of plasma entholin-1 levels in patients with stable coronary artery disease.