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Prognostic Value of Plasma Big Endothelin-1 Level among Patients with Three-Vessel Disease: A Cohort Study

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Aim: To evaluate the prognostic value of plasma big endothelin-1 level in the context of three-vessel disease (TVD) with heavy atherosclerotic burden.

Methods: A total of 6,150 patients with TVD and available big endothelin-1 data were included in the study. Participants were divided into two groups according to the optimal cutoff value of big endothelin-1 for mortality prediction. The primary endpoint was all-cause death. C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated to evaluate the added prognostic value of plasma big endothelin-1 level beyond the SYNTAX score Ⅱ.

Results: On the basis of the optimal cutoff value of 0.79 pmol/L, 1,984 patients were assigned to the high big endothelin-1 group. During a median follow-up of 6.8 years, 818 patients experienced all-cause death. Plasma big endothelin-1 level was significantly higher in patients who died than in patients who survived. Multivariable analysis found that high big endothelin-1 level was independently associated with an increased risk of mortality (hazard ratio: 1.36, 95% confidence interval: 1.18−1.57, $P<0.001$). The association of big endothelin-1 with all-cause death was relatively consistent across subgroups with no significant interactions. The predictive ability of the SYNTAX score Ⅱ was significantly enhanced by addition of plasma big endothelin-1 level (C-index: 0.723 vs. 0.715, $P=0.029$; NRI: 0.304, $P<0.001$; IDI: 0.009, $P<0.001$).

Conclusions: Plasma big endothelin-1 level is an independent predictor of long-term mortality in patients with TVD. It can improve the discrimination and reclassification of the SYNTAX score Ⅱ for mortality prediction.

Key words: Three-vessel coronary artery disease, Big endothelin-1, Prognosis

Introduction

Three-vessel disease (TVD), characterized by significant stenosis in all three major coronary arteries, is a severe form of coronary artery disease (CAD) that confers a substantial risk of mortality[1]. Risk stratification is important to identify high-risk patients with TVD who require intensive treatment and close fol-

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low-up. With this aim, the SYNTAX score (SS) and SYNTAX score Ⅱ (SSⅡ) have been established for risk assessment in patients with TVD[2, 3]. However, accurate risk stratification has always been challenging. Identification of additional biomarkers with prognostic significance may be able to improve the predictability of the established models.

Endothelin-1 (ET-1), a 21-amino acid peptide, is the most powerful constrictor of human vessels discovered to date[4]. It is primarily produced and released by vascular endothelial cells and can cause endothelial dysfunction and inflammation, which may contribute to atherosclerotic plaque formation[5]. However, clinical use of ET-1 as a biomarker is limited because of its instability in plasma[6]. As a precursor of ET-1, big ET-1 is relatively stable and can be used as an alternative approach for indirect estimation of ET-1 release[6]. Big ET-1 level was shown to be correlated with disease severity and clinical outcome in patients with acute myocardial infarction (MI) and stable CAD[7-10]. However, its clinical implications have not been evaluated in the setting of TVD with advanced coronary atheroma burden.

Aim

The present study aimed to assess the prognostic value of plasma big ET-1 level in patients with TVD.

Methods

Study Design and Participants

Data were obtained from a large prospective cohort study in which a total of 8,943 patients with TVD were consecutively enrolled from April 2004 to February 2011 at Fuwai Hospital, Chinese Academy of Medical Sciences (Beijing, China). Eligible patients were those who had TVD, defined as angiographically confirmed stenosis of ≥ 50% in all three main epicardial coronary arteries (left anterior descending, left circumflex, and right coronary arteries) with or without involvement of the left main artery, and were willing to undergo follow-up. There were no prespecified exclusion criteria. No treatment intervention was dictated by the protocol for the observational study. Patients received medical therapy (MT) alone, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) according to contemporary practice guidelines and their preferences[11, 12]. After enrollment, the patients were followed up in accordance with the study protocol. Baseline and procedural data for all participants were collected into a database by independent clinical research coordinators.

The study complied with the principles of the Declaration of Helsinki and was approved by the Review Board of Fuwai Hospital. Written informed consent was obtained from all participants.

Definitions

The concentrations of plasma big ET-1 were measured in fasting venous blood samples after admission for coronary angiography, using a highly sensitive and specific commercial sandwich enzyme immunoassay (BI-20082H; Biomedica, Wien, Austria). The SS was calculated using an online calculator (http://www.syntaxscore.com) by a dedicated research group blinded to the clinical data. Calculation of the SSⅡ was based on two anatomical variables and six clinical variables[3]. Creatinine clearance was calculated by the Cockcroft and Gault formula.

Outcomes

Outcome data were obtained by telephone interview, follow-up letter or clinic visit. All events were carefully checked and verified by an independent group of clinical physicians. Investigator training, blinded questionnaire filling, and telephone recording were performed to achieve high-quality results. The primary endpoint was all-cause death. Secondary endpoints included cardiac death, major adverse cardiac and cerebrovascular events (MACCE), a composite of all-cause death, MI, stroke, or unplanned revascularization, and the individual components of the composite. All deaths were considered cardiac unless an unequivocal noncardiac cause could be established.

Statistical Analysis

A receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value of plasma big ET-1 for mortality prediction (**Supplementary Fig. 1**). Participants were divided into high and low big ET-1 groups according to this cutoff value.

Summary statistics were presented as frequency and percentage for categorical variables and mean ± standard deviation or median and interquartile range for continuous variables. An independent-sample Student's *t*-test or the Mann−Whitney *U*-test was performed for comparisons of continuous variables, and the Pearson chi-square test or Fisher's exact test was performed for comparison of categorical variables.

Survival curves were constructed by the Kaplan−Meier method and compared by the log-rank test. Univariable and multivariable Cox proportional hazards regressions were performed to calculate the hazard ratio (HR) and 95% confidence interval (CI) and evaluate the associations between big ET-1 level (as a categorical or continuous variable normalized by $\log_{10}$

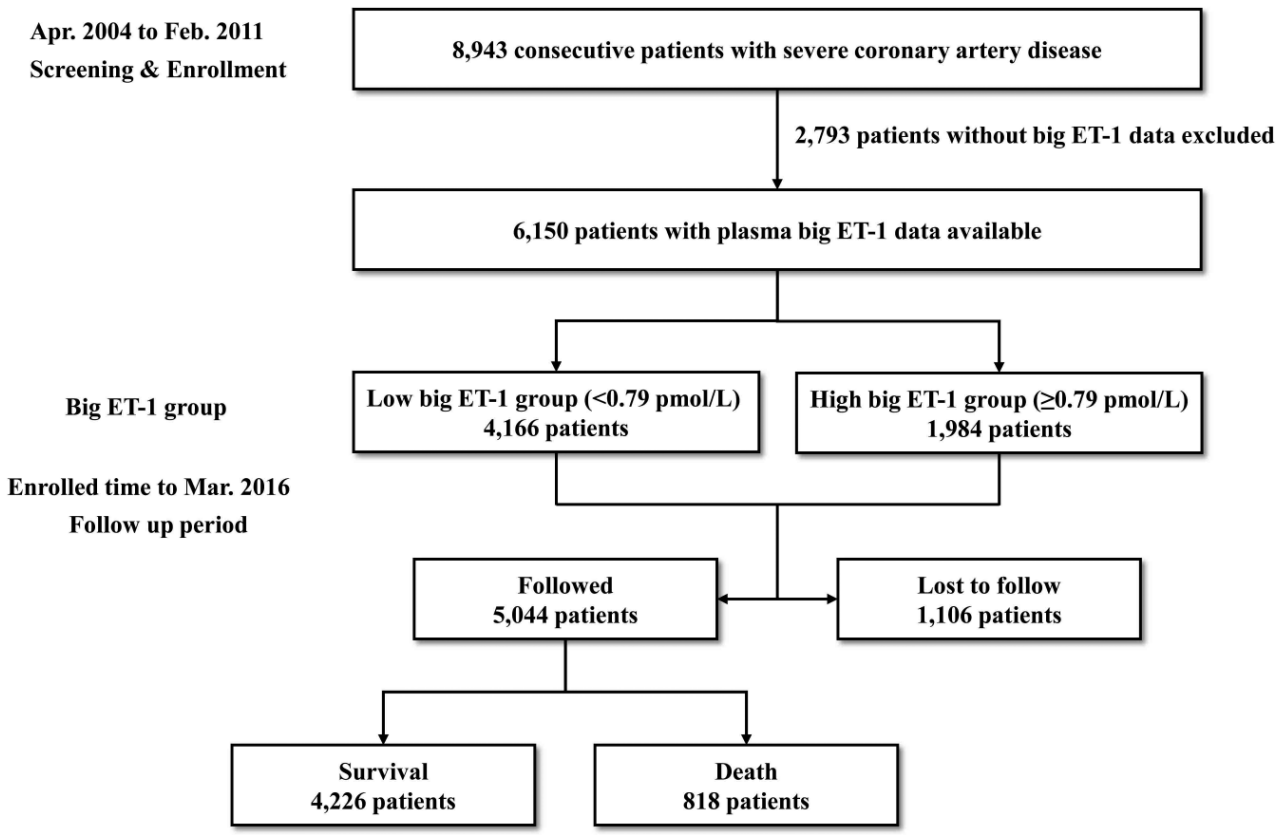

Fig. 1. Flowchart of subject selection.

transformation) and clinical outcomes. Covariates included in the multivariable model were age, sex, body mass index, hypertension, diabetes, previous MI, previous stroke, clinical presentation (stable angina pectoris [SAP] or acute coronary syndrome [ACS]), left main coronary artery involvement, left ventricular ejection fraction (LVEF), creatinine clearance, SS (≤22, 23−32, or ≥33), procedure (MT, PCI, or CABG), and aspirin. Patients who were lost to follow-up were censored at the last available contact.

Exploratory subgroup analyses of the primary outcome were performed according to age (<65 or ≥65 years), sex (male or female), diabetes (yes or no), presentation (SAP or ACS), left main involvement (yes or no), LVEF (<40% or ≥40%), SS (0−22, 23−32, or ≥33), and procedure (MT, PCI, or CABG). Interactions between plasma big ET-1 level (high or low) and these covariates were tested to interpret potential subgroup differences. The above-described multivariable Cox proportional hazards models were used for the interaction and subgroup analyses.

To assess the added prognostic value of big ET-1 for mortality prediction beyond the SSII, the C-index, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated using R software version 3.4.3 (R Core Team, Vienna, Austria).

Two-sided *P*-values of <0.05 were considered statistically significant. Analyses were performed using SPSS software version 22.0 (IBM, Armonk, NY, USA) unless otherwise stated.

Results

A total of 6,150 patients with available big ET-1 data were included in the present analysis. On the basis of the optimal cutoff value of 0.79 pmol/L, the patients were divided into low and high big ET-1 groups (**Fig. 1**). At baseline, patients in the high big ET-1 group were older and had higher troponin I, N-terminal pro-B-type natriuretic peptide, and high-sensitivity C-reactive protein, but lower LVEF and creatinine clearance (**Table 1**). Higher rates of female sex, hypertension, diabetes, previous MI, previous stroke, chronic kidney disease, and high SS were observed in the high big ET-1 group. Patients in the high big ET-1 group were more likely to receive MT alone rather than CABG and to take aspirin.

The median follow-up was 6.8 (5.7−8.1) years, with a response rate of 82.0% (**Fig. 1**). The baseline

Table 1. Baseline characteristics of the study population grouped by the optimal cutoff value of big endothelin-1

	Overall (n=6150)	Big ET-1 <0.79 pmol/L (n=4166)	Big ET-1 ≥0.79 pmol/L (n=1984)	P-value
Demographics				
Age, year	60.9±10.0	60.5±9.9	61.8±10.2	<0.001
Male	4924 (80.1)	3367 (80.8)	1557 (78.5)	0.032
BMI, kg/m^2	25.9±3.1	25.8±3.0	26.0±3.1	0.192
Medical history and risk factor				
Hypertension	4176 (67.9)	2785 (66.9)	1391 (70.1)	0.010
Diabetes	2189 (35.6)	1428 (34.3)	761 (38.4)	0.002
Hyperlipidemia	3691 (60.0)	2529 (60.7)	1162 (58.6)	0.110
Previous MI	2204 (35.8)	1454 (34.9)	750 (37.8)	0.027
Previous stroke	646 (10.5)	406 (9.7)	240 (12.1)	0.005
COPD	76 (1.2)	44 (1.1)	32 (1.6)	0.065
PAD	575 (9.3)	376 (9.0)	199 (10.0)	0.206
CKD	57 (0.9)	24 (0.6)	33 (1.7)	<0.001
Smoker	3392 (55.2)	2300 (55.2)	1092 (55.0)	0.901
Clinical characteristic				
SAP	2406 (39.1)	1662 (39.9)	744 (37.5)	0.072
ACS	3744 (60.9)	2504 (60.1)	1240 (62.5)	0.072
Left main involvement	1435 (23.3)	952 (22.9)	483 (24.3)	0.196
LVEF, %	58.3±9.5	58.9±8.9	57.2±10.4	<0.001
Big ET-1, pmol/L	0.65 (0.50–0.86)	0.56 (0.45–0.66)	1.05 (0.87–2.14)	<0.001
Troponin I, ng/mL	0.03 (0.01–0.09)	0.02 (0.01–0.07)	0.03 (0.02–0.14)	<0.001
NT-proBNP, pmol/L	632.0 (445.8–972.8)	596.1 (424.2–880.4)	715.4 (497.5–1241.4)	<0.001
hsCRP, mg/L	2.05 (1.00–5.45)	1.93 (0.96–4.70)	2.39 (1.08–6.93)	<0.001
Creatinine clearance, mL/min	86.7±27.5	87.9±27.0	84.1±28.5	<0.001
Procedural characteristic				
SYNTAX score				
≤22	2255 (36.7)	1570 (38.7)	685 (35.8)	0.027
23–32	2271 (36.9)	1534 (37.8)	737 (38.5)	0.642
≥33	1444 (23.5)	950 (23.4)	494 (25.8)	0.048
Treatment				
MT	1690 (27.5)	1073 (25.8)	617 (31.1)	<0.001
PCI	2576 (41.9)	1757 (42.2)	819 (41.3)	0.506
CABG	1884 (30.6)	1336 (32.1)	548 (27.6)	<0.001
Medication at discharge				
Aspirin	5908 (96.1)	4036 (96.9)	1872 (94.4)	<0.001
Clopidogrel	3328 (54.1)	2284 (54.8)	1044 (52.6)	0.105
ACEI	2215 (36.0)	1495 (35.9)	720 (36.3)	0.757
ARB	1013 (16.5)	671 (16.1)	342 (17.2)	0.264
Beta-blocker	5457 (88.7)	3694 (88.7)	1763 (88.9)	0.825
CCB	2097 (34.1)	1409 (33.8)	688 (34.7)	0.508
Statin	4149 (67.5)	2799 (67.2)	1350 (68.0)	0.502

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin Ⅱ receptor blockers; BMI, body mass index; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAD, peripheral artery disease.

characteristics of the patients followed up and lost to follow-up are listed in **Supplementary Table 1**. All patients included in the analysis completed at least one follow-up. During the follow-up period, 818 (13.3%) patients experienced all-cause death. The median level of plasma big ET-1 was significantly higher in the

Table 2. Risks of primary and secondary outcomes

Outcome	No. of Patients with event (%)	Crude HR (95% CI)	Crude *P*-value	Adjusted HR (95% CI)	Adjusted *P*-value
All-cause death					
Low big ET-1	443 (10.6)	Reference		Reference	
High big ET-1	375 (18.9)	1.69 (1.47−1.94)	<0.001	1.38 (1.19−1.59)	<0.001
log(big ET-1)	–	1.93 (1.55−2.40)	<0.001	1.43 (1.13−1.80)	0.002
Cardiac death					
Low big ET-1	231 (5.5)	Reference		Reference	
High big ET-1	204 (10.3)	1.75 (1.44−2.11)	<0.001	1.37 (1.13−1.67)	0.002
log(big ET-1)	–	2.11 (1.57−2.85)	<0.001	1.53 (1.11−2.10)	0.009
MACCE					
Low big ET-1	1067 (25.6)	Reference		Reference	
High big ET-1	695 (35.0)	1.32 (1.20−1.45)	<0.001	1.20 (1.09−1.32)	<0.001
log(big ET-1)	–	1.38 (1.18−1.62)	<0.001	1.20 (1.02−1.42)	0.027
Myocardial infarction					
Low big ET-1	180 (4.3)	Reference		Reference	
High big ET-1	105 (5.3)	1.13 (0.88−1.44)	0.335	1.12 (0.88−1.44)	0.358
log(big ET-1)	–	1.01 (0.69−1.48)	0.969	1.02 (0.69−1.50)	0.931
Stroke					
Low big ET-1	266 (6.4)	Reference		Reference	
High big ET-1	155 (7.8)	1.17 (0.96−1.43)	0.116	1.12 (0.92−1.38)	0.265
log(big ET-1)	–	1.13 (0.81−1.57)	0.469	1.06 (0.75−1.48)	0.746
Unplanned revascularization					
Low big ET-1	321 (7.7)	Reference		Reference	
High big ET-1	167 (8.4)	1.11 (0.92−1.34)	0.264	1.11 (0.92−1.35)	0.277
log(big ET-1)	–	1.08 (0.77−1.49)	0.663	1.12 (0.81−1.56)	0.494

patients who died (0.74 [0.54−1.08] pmol/L) than in those who survived (0.64 [0.50−0.84] pmol/L, $P<0.001$). Significantly more all-cause death, cardiac death, MACCE, and stroke occurred in the high big ET-1 group compared with the low big ET-1 group (all $P<0.05$, **Table 2**).

Univariable analysis showed that high big ET-1 level was associated with higher risks of all-cause death, cardiac death, and MACCE, but not MI, stroke, or unplanned revascularization (**Table 2**). After adjustment for covariates, high big ET-1 level remained an independent risk factor for all-cause death (HR: 1.36, 95% CI: 1.18−1.57, $P<0.001$), cardiac death (HR: 1.36, 95% CI: 1.12−1.66, $P=0.002$), and MACCE (HR: 1.19, 95% CI: 1.08−1.31, $P=0.001$). **Fig. 2** shows the Kaplan−Meier estimates for the primary and secondary endpoints (log-rank $P<0.001$ for all-cause death, cardiac death, and MACCE).

The relationship of big ET-1 level (high or low) with all-cause death was relatively consistent across the subgroups of age, sex, diabetes, presentation, left main disease, LVEF, SS, and procedure (**Fig. 3**). There were no significant interactions between big ET-1 levels and these covariates (interaction $P>0.1$ for all subgroups).

When big ET-1 level (high or low) was combined with the SSII for mortality prediction, there were significant improvements in C-index (0.723 [0.704−0.742] vs. 0.715 [0.697−0.734], $P=0.029$), NRI (0.304 [0.229−0.378], $P<0.001$), and IDI (0.009 [0.006−0.012], $P<0.001$) compared with the SSII alone (**Table 3**).

Discussion

The study shows that (i) high plasma big ET-1 level is an independent risk factor for all-cause death, cardiac death, and MACCE and is relatively consistent across subgroups and (ii) plasma big ET-1 level improves predictability of the SSII for long-term mortality in patients with TVD.

Plasma big ET-1 level has been identified as a novel marker of disease severity and clinical outcome in the context of CAD. Big ET-1 level was a predictor of severity in stable CAD, as reflected by the Gensini score[9]. Moreover, two cohort studies found that high big ET-1 level was associated with increased risks of adverse outcomes in patients with stable CAD[8, 10]. In another cohort study of 983 patients with acute MI,

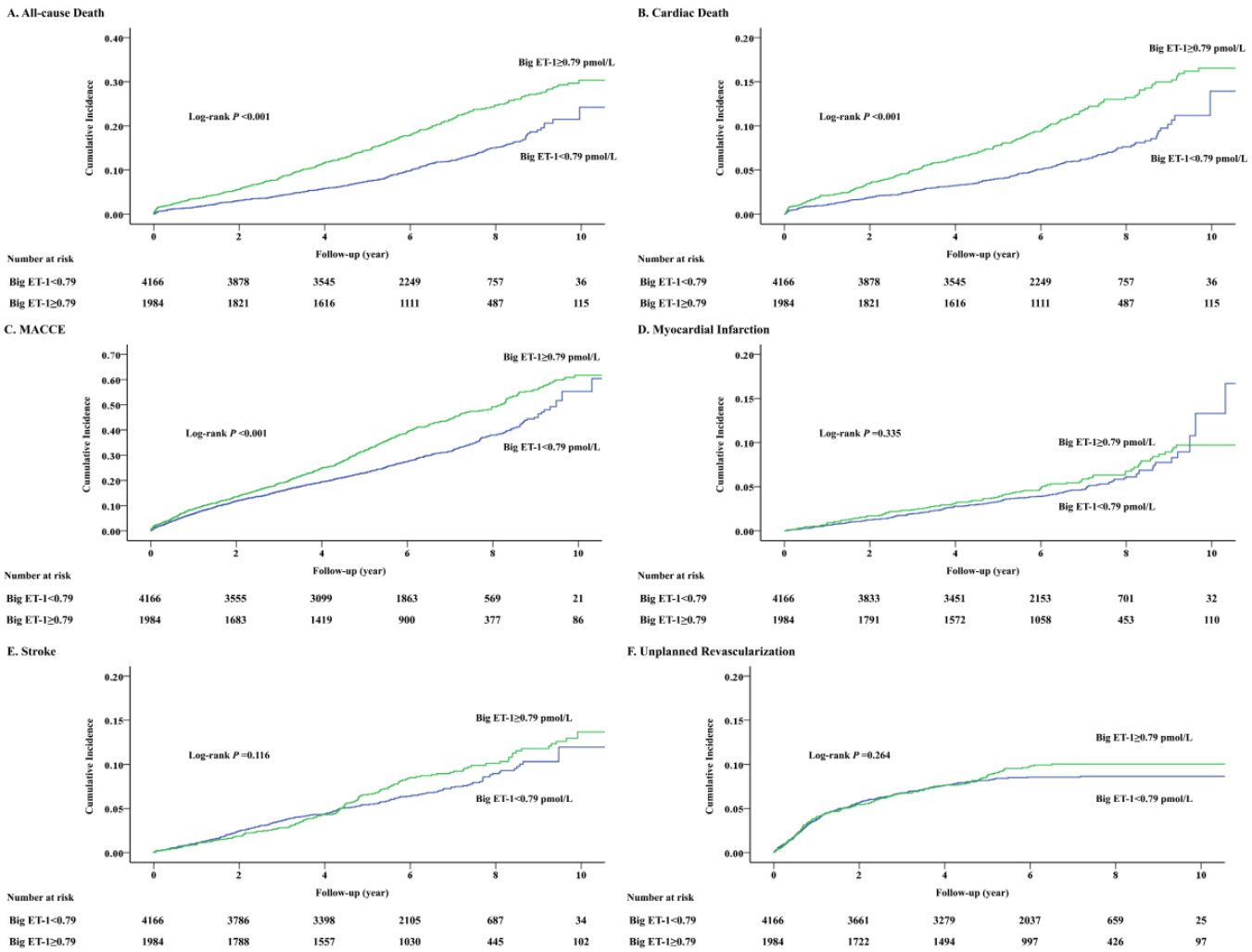

Fig. 2. Cumulative incidence curves for primary and secondary endpoints.

(A–F) Cumulative incidences of all-cause death (A), cardiac death (B), MACCE (C), myocardial infarction (D), stroke (E), and unplanned revascularization (F).

big ET-1 level was an independent predictor of death or heart failure, with an area under the ROC curve of 0.76[7]. These studies demonstrated that higher level of big ET-1 was associated with higher risks of adverse events in stable CAD or ACS, in accordance with the present study performed in SAP and ACS patients. The present study further extended the association to the setting of TVD with heavy atherosclerotic burden.

Revascularization (PCI or CABG) has been considered to improve prognosis in patients with multivessel disease compared with MT alone[13]. It remains unknown whether there is an interaction between treatment (MT, PCI, or CABG) and big ET-1 level with outcomes. In our study, the association between big ET-1 level and mortality was relatively consistent across patients receiving MT, PCI, and CABG, with no significant interaction between big ET-1 level and treatment. Thus, high big ET-1 level remained an independent risk marker for mortality regardless of whether or not revascularization was performed.

ET-1 contributes to the poor prognosis in TVD patients through several mechanisms. First, as a vasoconstrictor, ET-1 accounts for nearly all the resting tone in atherosclerotic coronary arteries[14]. High ET-1 level can lead to vasoconstriction and decreased coronary blood flow, which may induce or aggravate myocardial ischemia. Second, ET-1 can decrease nitric oxide (NO) production and increase NO degradation, leading to an imbalance between NO and ET-1 and subsequent endothelial dysfunction in the coronary circulation[15]. Third, ET-1 can promote increases in oxidative stress and inflammatory cell infiltration, which contribute to atherosclerotic plaque formation, progression, and rupture[16]. These effects can be even more

	Low big ET-1	High big ET-1	Hazard ratio (95% confidence interval)	*P*-value for interaction
	no. of patients with all-cause death/total no. (%)			
Overall	443/4166 (10.6)	375/1984 (18.9)	1.38 (1.19–1.59)	
Age				0.524
<65 years	152/2623 (5.8)	131/1119 (11.7)	1.50 (1.17–1.91)	
⩾65 years	291/1543 (18.9)	244/865 (28.2)	1.30 (1.09–1.56)	
Sex				0.935
Male	355/3367 (10.5)	292/1557 (18.8)	1.38 (1.17–1.62)	
Female	88/799 (11.0)	83/427 (19.4)	1.31 (0.96–1.79)	
Diabetes				0.558
Yes	177/1428 (12.4)	168/761 (22.1)	1.41 (1.13–1.76)	
No	266/2738 (9.7)	207/1223 (16.9)	1.34 (1.11–1.62)	
Presentation				0.266
SAP	152/1662 (9.1)	110/744 (14.8)	1.23 (0.95–1.59)	
ACS	291/2504 (11.6)	265/1240 (21.4)	1.47 (1.24–1.75)	
Left main disease				0.384
Yes	115/952 (12.1)	109/483 (22.6)	1.53 (1.16–2.00)	
No	328/3214 (10.2)	266/1501 (17.7)	1.32 (1.11–1.56)	
Ejection fraction				0.700
<40%	40/160 (25.0)	66/159 (41.5)	1.58 (1.04–2.38)	
⩾40%	403/4006 (10.1)	309/1825 (16.9)	1.35 (1.16–1.57)	
SYNTAX score				0.214
0-22	135/1570 (8.6)	103/685 (15.0)	1.32 (1.01–1.71)	
23-32	170/1534 (11.1)	128/737 (17.4)	1.24 (0.98–1.57)	
⩾33	124/950 (13.1)	125/494 (25.3)	1.64 (1.27–2.12)	
Procedure				0.618
MT	206/1073 (19.2)	198/617 (32.1)	1.48 (1.21–1.82)	
PCI	141/1757 (8.0)	109/819 (13.3)	1.29 (0.99–1.67)	
CABG	96/1336 (7.2)	68/548 (12.4)	1.27 (0.91–1.76)	

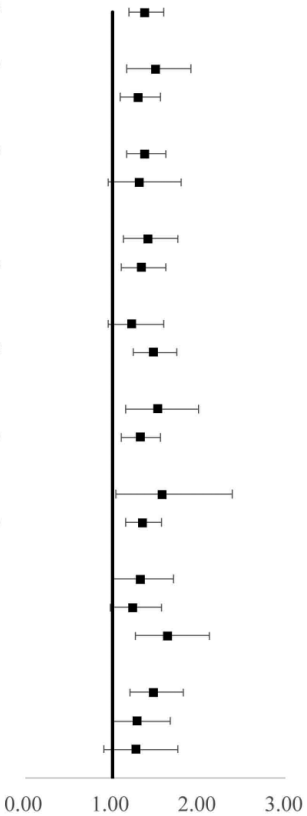

Fig. 3. Subgroup analyses for the primary endpoint.

HRs and 95% CIs were calculated by reference to the low big ET-1 group. The interaction between big ET-1 level and each covariate was tested by a multivariable Cox proportional hazards regression model.

significant and more likely to lead to adverse events in the setting of TVD with heavy atherosclerotic burden in all three major vessels. Compared with traditional biomarkers representing myocardial injury (troponin I), cardiac stress (N-terminal pro-B-type natriuretic peptide), and inflammation (high-sensitivity C-reactive protein), big ET-1 can reflect endothelial function that is important for the development of atherosclerosis[4].

TVD is present in 20%−30% of patients with obstructive CAD[17, 18]. As a severe type of CAD, it confers an almost two-fold higher risk of mortality compared with single-vessel disease[1]. Calculation of the SS is recommended for assessment of the long-term mortality risk in TVD patients[19] but showed only modest predictability in previous studies[20, 21]. Despite the generally better performance of the SSII compared with the SS, some studies found only a moderate discrimination ability of the SSII for long-term mortality prediction in patients with multivessel disease[22, 23]. Biomarkers have been shown to provide additional prognostic information beyond clinical characteristics in CAD[24]. Addition of biomarkers to the SSII may enhance its predictability, because it is mainly based on clinical characteristics. Our study demonstrated significant improvements in the C-index, NRI, and IDI after incorporation of big ET-1 level into the SSII, indicating better predictive performance compared with the SSII alone. These findings are of great importance because better risk stratification can be achieved for guidance of treatment. Furthermore, similar to the traditional biomarkers, measurement of plasma big ET-1 is simple and economic using a commercial immunoassay. Although more evidence is needed regarding the prognostic value of big ET-1 level, our study has shown the feasibility of its addition to the established model to improve predictability.

There are some limitations that should be noticed in this study. First, this was an observational study that

Table 3. Additional prognostic information provided by big endothelin-1 level beyond SSII

	C-index (95% CI)	*P*-value	NRI (95% CI)	*P*-value	IDI (95% CI)	*P*-value
SSII	0.715 (0.697−0.734)	Reference	−	Reference	−	Reference
SSII + big ET-1	0.723 (0.704−0.742)	0.029	0.304 (0.229−0.378)	<0.001	0.009 (0.006−0.012)	<0.001

may suffer from potential selection and measurement biases. Second, all participants in the study were enrolled from a single specialized center for cardiovascular disease, which may limit the reliability and generalizability of our findings. Third, angiographic criteria were used as the main indications for revascularization, and physiological tests were only performed when a treatment decision could not be made using the angiographic findings alone. As a result, most of the participants in our study did not undergo preprocedural/intraprocedural ischemia evaluations. Fourth, the present analyses were based on a single plasma big ET-1 measurement, and thus, potential fluctuations in its levels remain uncountable.

Conclusions

In patients with TVD, plasma big ET-1 level was significantly higher in patients who died during follow-up than those who survived. Higher big ET-1 level was independently associated with increased risks of all-cause death, cardiac death, and MACCE. Big ET-1 level improves the discrimination and reclassification of the SSII to predict long-term mortality.

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Conflict of Interest

Dr. Lei Song reports grants from the CAMS Innovation Fund for Medical Sciences (CAMS-I2M, 2016-I2M-1-002), National High Technology Research and Development Program of China (2015AA020407), and National Natural Science Foundation of China (81470380). The other authors have nothing to disclose.

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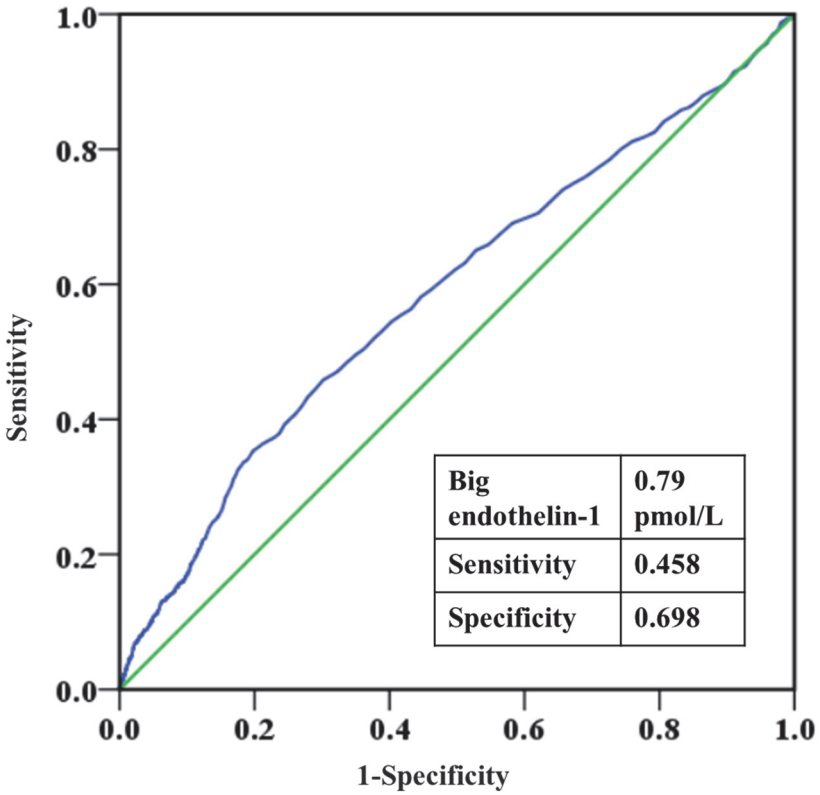

Supplementary Fig. 1. Receiver operating characteristic (ROC) curve of big endothelin-1 for mortality prediction.

Supplementary Table 1. Baseline characteristics of patients followed up and lost to follow up.

	Patients followed up (n=5,044)	Patients lost to follow up (n=1,106)	P-value
Demographics			
Age, year	60.7±9.9	62.0±10.3	<0.001
Male	4048 (80.3)	876 (79.2)	0.429
BMI, kg/m^2	25.9±3.0	25.6±3.3	0.003
Medical history and risk factor			
Hypertension	3434 (68.1)	742 (67.1)	0.522
Diabetes	1753 (34.8)	436 (39.4)	0.003
Hyperlipidemia	3110 (61.7)	581 (52.5)	<0.001
Previous MI	1748 (34.7)	456 (41.2)	<0.001
Previous stroke	505 (10.0)	141 (12.7)	0.007
COPD	62 (1.2)	14 (1.3)	0.920
PAD	456 (9.0)	119 (10.8)	0.075
CKD	31 (0.6)	26 (2.4)	<0.001
Smoker	2788 (55.3)	604 (54.6)	0.688
Clinical characteristic			
SAP	1988 (39.4)	418 (37.8)	0.318
ACS	3056 (60.6)	688 (62.2)	0.318
Left main involvement	1131 (22.4)	304 (27.5)	<0.001
LVEF, %	58.7±9.2	56.7±10.3	<0.001
Big ET-1, pmol/L	0.65 (0.50–0.85)	0.68 (0.52–1.01)	<0.001
Troponin I, ng/mL	0.03 (0.01–0.08)	0.03 (0.02–0.13)	<0.001
NT-proBNP, pmol/L	622.2 (443.2–939.4)	690.9 (462.0–1228.1)	<0.001
hsCRP, mg/L	2.01 (0.98–5.27)	2.29 (1.05–6.19)	0.015
Creatinine clearance, mL/min	87.5±27.5	83.0±27.4	<0.001
Procedural characteristic			
SYNTAX score			
≤22	1905 (37.8)	350 (31.6)	<0.001
23–32	1841 (36.5)	430 (38.9)	0.137
≥33	1148 (22.8)	296 (26.8)	0.004
Treatment			
MT	1295 (25.7)	395 (35.7)	<0.001
PCI	2168 (43.0)	408 (36.9)	<0.001
CABG	1581 (31.3)	303 (27.4)	0.010
Medication at discharge			
Aspirin	4871 (96.6)	1037 (93.8)	<0.001
Clopidogrel	2758 (54.7)	570 (51.5)	0.058
ACEI	1801 (35.7)	414 (37.4)	0.279
ARB	816 (16.2)	197 (17.8)	0.185
Beta-blocker	4469 (88.6)	988 (89.3)	0.486
CCB	1681 (33.3)	416 (37.6)	0.006
Statin	3388 (67.2)	761 (68.8)	0.292

Values are presented as mean±standard deviation, median (interquartile) or number (%).
ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin Ⅱ receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ET-1, endothelin-1; hsCRP, high sensitivity C reactive protein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MT, medical therapy; NT-proBNP, N-terminal pro-B-Type natriuretic peptide; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SAP, stable angina pectoris.