Prognostic Value of Combination of Plasma D-Dimer Concentration and Estimated Glomerular Filtration Rate in Predicting Long-Term Mortality of Patients With Stable Coronary Artery Disease

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Background: A modestly elevated circulating D-dimer level may be relevant to coronary artery disease (CAD), but its prognostic value, both independently and in combination with estimated glomerular filtration rate (eGFR), for long-term death has not been fully evaluated in stable CAD patients.

Methods and Results: Baseline plasma D-dimer levels and eGFR were measured in 1,341 outpatients (mean age: 65 years) with prior myocardial infarction (MI), coronary revascularization, and/or angiographic evidence of a significant stenosis (>50%) for at least one of the major coronary arteries. Among these patients, 43% had prior MI, 47% had prior coronary revascularization, 41% had multivessel CAD, 14% had paroxysmal or persistent atrial fibrillation, 32% had diabetes, and 32% had chronic kidney disease (eGFR <60 mL/min/1.73 m²). D-dimer levels weakly correlated with eGFR (r=−0.25; P<0.0001). During a mean follow-up period of 73 months, there were 124 deaths, including 61 cardiovascular deaths. Multivariate Cox regression analysis identified D-dimer levels (P=0.001) and eGFR (P=0.006) as independent predictors of all-cause death. Adding both D-dimer and eGFR to a baseline model with established risk factors improved the net reclassification (P<0.005) and integrated discrimination improvement (P<0.05) greater than that of any single biomarker or baseline model alone.

Conclusions: The combinatorial value of assessing D-dimer levels and eGFR may provide useful insight regarding stable CAD patients’ long-term risk stratification.

Key Words: Chronic kidney disease; Coronary artery disease; D-dimer; Prognosis

Simple and accurate risk stratification for cardiovascular death in patients with stable coronary artery disease (CAD) is critical in facilitating secondary preventive therapy. The use of traditional risk factors and simple clinical information does not fully explain the risk of death in patients with stable CAD. Moreover, a single biomarker may not adequately assess the risk. Thus, combined assessments may improve risk stratification in patients with stable CAD.

D-dimer is the endproduct of the plasmin-mediated degradation of cross-linked fibrin. Plasma concentrations of D-dimer, a marker of coagulation state, are dependent on fibrin generation and subsequent degradation by the endogenous fibrinolytic system. Various disorders with excessive activation of the coagulation system, such as acute venous thromboembolism, present with highly elevated D-dimer levels. It has been suggested that a modestly elevated circulating D-dimer level reflects minor increases in blood coagulation, thrombin formation, and turnover of cross-linked intravascular fibrin (which is partly intra-arterial in origin). Such increases may be relevant to CAD. Previous studies have shown that increased metabolism of cross-linked fibrin in arteriosclerotic plaques leads to an increase in plasma D-dimer concentration. Increased D-dimer levels are reported to be proportional to the severity of arteriosclerosis in patients with stable CAD and peripheral arterial occlusive disease. However, the prognostic value of modestly elevated plasma D-dimer levels has not been fully eval-
uated in patients with stable CAD.

The measurement of the estimated glomerular filtration rate (eGFR) is now an integral part of daily clinical practice, and routinely used to evaluate and monitor renal function. In patients with stable CAD, concomitant chronic kidney disease (CKD; eGFR <60 mL/min/1.73 m²) is a common condition and substantially increases morbidity and mortality as an independent risk factor.

Therefore, in the present study, we prospectively investigated the prognostic value of D-dimer, both independently and in combination with eGFR, for long-term death of outpatients with stable CAD.

Methods

Study Population
This prospective study was conducted at the Department of Cardiology, Fujiita Health University School of Medicine (Toyoake, Japan). Between July 2006 and July 2008, we enrolled 1,341 outpatients (mean age: 65 years, range 35–88 years) with stable CAD. Inclusion criteria were prior myocardial infarction (MI), coronary revascularization (percutaneous coronary revascularization and/or coronary artery bypass graft surgery), and/or angiographic evidence of a significant stenosis (>50%) of ≥1 major coronary arteries. Patients with the following conditions were excluded from this study: (a) recent acute coronary syndrome (ACS) or coronary revascularization (within the 6 months prior to enrollment), (b) New York Heart Association functional class IV or severe class III heart failure (HF), (c) moderate or severe valvular heart disease, (d) stage 5 CKD (eGFR <15 mL/min/1.73 m²), (e) venous thrombosis or pulmonary embolism, (f) acute infectious disease, (g) aortic aneurysm or dissection, (h) active malignant disease treated with chemotherapy or radiation, or (i) disseminated intravascular coagulation.

The patients’ clinical characteristics were obtained from their medical records upon enrollment. CKD was defined as an eGFR <60 mL/min/1.73 m². Diabetes was defined as a history or presence of diabetes and/or a fasting plasma glucose level ≥126 mg/dL, hemoglobin A1c value ≥6.5%, or the presence of diabetic retinopathy. Hypertension was defined as satisfying at least one of the following criteria: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or history of antihypertensive treatment. Dyslipidemia was defined as total cholesterol level ≥220 mg/dL or a history of lipid-lowering therapy. Smoking history was defined as either a current smoker or ex-smoker. The 2D echocardiography was performed by experts blinded to the study, and the left ventricular ejection fraction (LVEF) was calculated using the modified Simpson’s method.

Measurement of Biomarkers
Blood samples for baseline measurements of biomarkers were collected, centrifuged at 1,000 g at 4°C for 15 min to isolate plasma and serum, and stored at −80°C until samples were assayed. Plasma D-dimer levels were measured with a latex-enhanced photometric immunosassay (LPIA-ACE D-Dimer, LSI Medience Corporation, Tokyo, Japan). Serum high-sensitivity C-reactive protein (hsCRP) levels were measured using a latex-enhanced hsCRP immunosassay (N-Latex CRP II, Siemens Healthineers Japan, Tokyo, Japan). Serum creatinine levels were determined routinely with an enzymatic method using Liquitech® Creatinine PAP II (Roche Diagnostics, Tokyo, Japan). The eGFR was calculated by the Modification of Diet in Renal Disease Study equation, which is recommended by the Japan Chronic Kidney Disease Initiative.

Follow-up Study
Patients were prospectively followed up until June 2014. Physicians, who were blinded to D-dimer level, independently selected the appropriate therapy. The primary endpoint was all-cause death. The secondary endpoint was cardiovascular death (e.g., death from MI, HF, arrhythmia, sudden death, or stroke). Data for the endpoints were obtained from hospital charts and through telephone interviews with patients. The telephone interviews were conducted by trained reviewers who were blinded to the patient D-dimer levels.

Ethics
This study was approved by the Ethics Committee of Fujiita Health University and was conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent for participation.

Statistical Analysis
Statistical analyses were performed with StatFlex version 6 (Artech Co. Ltd., Osaka, Japan). Normally distributed variables are expressed as mean values ± standard deviations, and nonparametric data are presented as medians and interquartile ranges. Given the skewed distributions of the D-dimer and hsCRP data, analyses were performed after log-transformation of these variables, which met the criteria for use in normalized statistical approaches after statistical confirmation. Intergroup differences were evaluated using one-way analysis of variance or the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. Intergroup differences in survival were examined using the Kaplan-Meier method and were compared by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated for each factor through the Cox proportional hazards analysis. All baseline variables with a P-value <0.05 in the univariate analyses were entered into the Cox multivariate model to determine independent predictors of the endpoint.

To assess whether the accuracy of predicting death would improve after adding both D-dimer and eGFR or each single biomarker into a baseline model with established risk factors (i.e., age, sex, hypertension, dyslipidemia, diabetes, smoking status, paroxysmal or persistent atrial fibrillation (AF), previous MI, and previous coronary revascularization), we calculated the C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The C-index is defined as the area under receiver-operating characteristic curves between individual predictive probabilities for death and the incidence of death, and was compared with respect to the baseline and enriched models containing the established risk factors as well as both D-dimer and eGFR or each single biomarker, respectively. NRI indicates relatively how many patients improved their predicted probability of death, and IDI represents the average improvement in predicted probability of death after adding variables into the baseline model. P<0.05 was considered statistically significant.
Results

Baseline Characteristics

Patient demographics and patient characteristics according to tertiles of D-dimer levels are listed in Table 1. The mean age of the study population was 65 years, and 78% of the patients were male. Among all patients, 43% had a history of previous MI, 47% had a history of coronary revascularization, 41% had multivessel CAD, 14% had paroxysmal or persistent AF, 32% had diabetes, and 32% had stage 3–4 CKD. The median (25th–75th percentile) D-dimer level was 0.43 (0.25–0.78) µg/mL and this level was higher in women [0.50 (0.31–0.85) µg/mL] than in men [0.42 (0.24–0.77) µg/mL, P=0.002].

Higher D-dimer levels were significantly associated with older age, higher prevalence of diabetes, previous MI, paroxysmal or persistent AF, multivessel CAD, and CKD, lower prevalence of dyslipidemia and male sex, more frequent use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers or β-blockers, higher hsCRP levels, lower frequency of statin use, and lower levels of hemoglobin, eGFR, and LVEF (Table 1). Moreover, D-dimer levels were found to weakly correlate with age (r=0.32, P<0.0001), hemoglobin levels (r=-0.29, P<0.0001), eGFR (r=-0.25, P<0.0001), and hsCRP levels (r=0.18, P<0.0001).

Prognostic Value of Biomarkers

During a mean follow-up period of 73 months after enrollment, there were 124 (9.2%) all-cause deaths, including 61 cardiovascular deaths. The causes of cardiovascular deaths were HF in 33 patients, MI in 14, stroke in 11, sudden death in 2, and arrhythmia in 1. Patients who died were older, had a lower prevalence of dyslipidemia, a higher prevalence of diabetes, paroxysmal or persistent AF and CKD, higher levels of D-dimer and hsCRP, and lower levels of hemoglobin, eGFR, and LVEF compared with survivors (Table 2). Patients who died also used antiplatelet or statin drugs less frequently than survivors.

Patients were divided into tertiles on the basis of D-dimer levels (1st, <0.32 µg/mL; 2nd, 0.32–0.61 µg/mL; and 3rd, >0.61 µg/mL). The Kaplan-Meier curves according to D-dimer tertiles revealed a graded increase in the risk of all-cause and cardiovascular death with higher D-dimer levels (both, P<0.0001; Figure 1). When patients were also divided into 2 groups according to the presence of CKD (eGFR <60 mL/min/1.73 m²), CKD patients had higher risks for all-cause and cardiovascular death than non-CKD patients (both, P<0.0001; Figure 2).

In the Cox multivariate analysis, including all baseline variables with P<0.05, as determined by univariate analysis (i.e., D-dimer either as continuous variable or as variable categorized into tertiles, eGFR either as continuous

| Table 1. Baseline Characteristics of Study Population of Stable CAD Patients According to Tertiles of D-Dimer |
|--------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| D-dimer tertile (µg/mL) | All | 1st (<0.32) | 2nd (0.32–0.61) | 3rd (>0.61) | P value for linear trend |
| n | 1,341 | 450 | 446 | 445 | <0.0001 |
| Age (years) | 65.4±10.1 | 61.5±10.2 | 66.0±9.1 | 68.7±9.5 | 0.0001 |
| Male (%) | 78 | 83 | 75 | 76 | 0.006 |
| Hypertension (%) | 64 | 63 | 64 | 66 | 0.39 |
| Dyslipidemia (%) | 61 | 64 | 64 | 56 | 0.01 |
| Diabetes (%) | 32 | 27 | 35 | 34 | 0.01 |
| Current or ex-smoker (%) | 47 | 48 | 46 | 45 | 0.36 |
| Previous MI (%) | 43 | 40 | 42 | 48 | 0.01 |
| Paroxysmal or persistent AF (%) | 14 | 12 | 14 | 16 | 0.07 |
| Previous coronary revascularization (%) | 47 | 47 | 44 | 50 | 0.37 |
| Multivessel disease (%) | 41 | 35 | 45 | 44 | 0.004 |
| WBC count (×10³/µL) | 6.2±2.6 | 6.0±1.6 | 6.2±1.7 | 6.3±3.8 | 0.13 |
| Hemoglobin (g/dL) | 13.5±1.7 | 13.9±1.5 | 13.6±1.6 | 12.8±1.7 | <0.0001 |
| Platelet count (×10³/µL) | 20.7±6.4 | 20.6±5.1 | 20.7±6.9 | 20.9±7.1 | 0.68 |
| eGFR (mL/min/1.73 m²) | 68.3±19.0 | 73.4±18.0 | 69.0±17.7 | 62.3±19.5 | <0.0001 |
| CKD (%) | 32 | 21 | 31 | 44 | <0.0001 |
| LDL-C (mg/dL) | 117.3±32.1 | 116.7±30.3 | 117.2±31.1 | 117.8±34.7 | 0.99 |
| hsCRP (mg/L) | 1.90 (0.70–2.00) | 1.30 (0.40–2.00) | 2.00 (0.70–2.00) | 2.00 (0.80–2.80) | <0.0001 |
| LVEF (%) | 53.4±11.3 | 54.8±10.1 | 54.0±11.9 | 51.4±11.7 | <0.0001 |

Data are mean ± standard deviation, percentage, or median (interquartile range). AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; WBC, white blood cell.
D-Dimer and GFR in Stable CAD

Discrimination and Reclassification of the Combination of D-Dimer and eGFR for Mortality Prediction

Reclassification of patients who died or were alive at follow-up is presented by the NRI. The addition of both D-dimer and eGFR to a baseline model with established risk factors significantly (all \( P<0.005 \)) improved the reclassification of patients beyond that of any single biomarker or the baseline model alone (Table 5). In addition, IDI improved (all \( P<0.05 \)) after adding both D-dimer and eGFR better than with any single biomarker or baseline model alone. However, the C-index did not improve after adding both D-dimer and eGFR beyond the baseline model alone because the C-statistic is insensitive for comparing the models. Similar results were seen for cardiovascular death (Table 5).

Discussion

The major findings of this prospective study were as follows. First, both D-dimer and eGFR were independent predictors of long-term all-cause and cardiovascular mortality rates (all \( P<0.0001 \); Figure 3).

**Table 2. Demographic and Clinical Variables of Survivors and Non-Survivors Among Stable CAD Patients**

| Variable                         | Survivors | Non-survivors | P value |
|----------------------------------|-----------|---------------|---------|
| n                                | 1,217     | 124           |         |
| Age (years)                      | 64.9±10.0 | 70.1±9.5      | \(<0.0001\) |
| Male (%)                         | 78        | 78            | 0.97    |
| Hypertension (%)                 | 65        | 63            | 0.71    |
| Dyslipidemia (%)                 | 63        | 49            | 0.004   |
| Diabetes (%)                     | 31        | 40            | 0.04    |
| Current or ex-smoker (%)         | 46        | 51            | 0.31    |
| Previous MI (%)                  | 43        | 48            | 0.22    |
| Paroxysmal or persistent AF (%)  | 13        | 22            | 0.005   |
| Previous coronary revascularization (%) | 47  | 51            | 0.40    |
| Multivessel disease (%)          | 41        | 48            | 0.13    |
| WBC count (×10⁹/L)               | 6.2±2.6   | 6.3±2.1       | 0.56    |
| Hemoglobin (g/dL)                | 13.5±1.6  | 12.8±2.2      | \(<0.0001\) |
| Platelet count (×10⁹/μL)         | 20.8±6.1  | 20.5±9.1      | 0.62    |
| eGFR (mL/min/1.73 m²)            | 69.3±18.5 | 58.4±20.5     | \(<0.0001\) |
| CKD (%)                          | 30        | 54            | \(<0.0001\) |
| LDL-C (mg/dL)                    | 117.0±32.2| 119.5±30.9  | 0.40    |
| D-dimer (µg/mL)                  | 0.42 (0.25–0.71) | 0.83 (0.45–1.42) | \(<0.0001\) |
| hsCRP (mg/L)                     | 1.90 (0.60–2.00) | 2.00 (1.00–3.00) | 0.005   |
| LVEF (%)                         | 53.9±10.9 | 48.6±13.8     | \(<0.0001\) |
| Treatment at enrollment (%)      |           |               |         |
| Antiplatelet drugs               | 83        | 73            | 0.005   |
| Statins                          | 60        | 46            | 0.003   |
| ACEI and/or ARB                  | 69        | 76            | 0.10    |
| β-blockers                       | 48        | 57            | 0.06    |
| Calcium channel blockers         | 37        | 38            | 0.82    |
| Anticoagulant drugs              | 10        | 10            | 0.97    |

Data are mean±standard deviation, percentage, or median (interquartile range). Abbreviations as in Table 1.

variable or as categorized variable according to CKD, age, dyslipidemia, diabetes, paroxysmal or persistent AF, hemoglobin, hsCRP, and LVEF), both D-dimer and eGFR were found to be independent predictors of all-cause death either as continuous variables (HR 2.00 per 10-fold increment, 95% CI: 1.32–3.05, \( P=0.001 \) and HR 0.86 per 10 mL/min/1.73 m² increment, 95% CI: 0.78–0.96, \( P=0.006 \), respectively) or as categorized variables (HR 2.62, 95% CI: 1.48–4.64, \( P=0.0009 \) for 3rd vs. 1st tertiles and HR 1.59, 95% CI: 1.09–2.32, \( P=0.02 \) for CKD vs. non-CKD, respectively; Table 4). Similar results were obtained for cardiovascular death (Table 4). In addition to D-dimer and eGFR, age and LVEF remained significantly associated with all-cause death. Paroxysmal or persistent AF and LVEF also remained significantly associated with cardiovascular death.

Combination of D-Dimer and eGFR

In the Cox multivariate analysis, including all baseline variables with \( P<0.05 \), as determined by the univariate analysis, the combination of D-dimer tertile and CKD was found to be an independent predictor of all-cause death (HR 4.19, 95% CI: 2.02–8.71, \( P=0.001 \) for CKD patients in the 3rd tertile of D-dimer vs. non-CKD patients in the 1st tertile of D-dimer; Table 4). Similar results were obtained for cardiovascular death (Table 4). In addition to D-dimer and eGFR, age and LVEF remained significantly associated with all-cause death. Paroxysmal or persistent AF and LVEF also remained significantly associated with cardiovascular death. The combination of D-dimer tertile and CKD was strongly associated with all-cause and cardiovascular mortality rates (all \( P<0.0001 \); Figure 3).
long-term all-cause and cardiovascular death. Considering the weak correlation between D-dimer and eGFR, this suggests that markers of coagulation status and renal function reflect different pathophysiological aspects of cardiovascular disease and may identify different groups of patients at risk. It is reasonable to expect that CKD patients who have the highest coagulation state are at greatest risk. Indeed, patients with both CKD and in the 3rd tertile of D-dimer had approximately 4.19- and 12.7-fold higher risk for all-cause and cardiovascular death, respectively, compared with non-CKD patients in the 1st tertile of D-dimer. These biomarkers are easily accessible and are, thus, readily measurable and relatively inexpensive to assay; in addition, the assays are reproducible and highly sensitive and specific. The combination of D-dimer and eGFR may be used as a part of an algorithm for assessing the long-term prognosis of stable CAD patients.

Combination of D-Dimer and eGFR

Atherothrombosis is defined as a ruptured atherosclerotic plaque with a thrombosis. The formation of an occlusive thrombus can lead to MI and stroke. Large, prospective studies have shown that higher plasma levels of D-dimer may be associated with the risk of thrombotic events, particularly stroke, in general populations and in patients with AF. Furthermore, Moss and coworkers demonstrated an independent association of D-dimer levels 2 months after acute MI with an increased risk of recurrent infarction in patients. Thus, D-dimer, a marker of coagulation status, may be closely associated with thrombotic events. On the other hand, while CKD is a risk multiplier for the development of cardiovascular disease, the largest hazard occurs for HF, which is also the leading cause of death among the cardiovascular diseases in patients with CKD. Thus, a combined assessment of D-dimer and eGFR may be expected to improve the prediction of long-term death beyond D-dimer or eGFR alone in patients with CAD.

We demonstrated that the combination of D-dimer and eGFR, which independently predicted CAD prognosis, improved the risk reclassification and discrimination for long-term all-cause and cardiovascular death. Considering the weak correlation between D-dimer and eGFR, this suggests that markers of coagulation status and renal function reflect different pathophysiological aspects of cardiovascular disease and may identify different groups of patients at risk. It is reasonable to expect that CKD patients who have the highest coagulation state are at greatest risk. Indeed, patients with both CKD and in the 3rd tertile of D-dimer had approximately 4.19- and 12.7-fold higher risk for all-cause and cardiovascular death, respectively, compared with non-CKD patients in the 1st tertile of D-dimer. These biomarkers are easily accessible and are, thus, readily measurable and relatively inexpensive to assay; in addition, the assays are reproducible and highly sensitive and specific. The combination of D-dimer and eGFR may be used as a part of an algorithm for assessing the long-term prognosis of stable CAD patients.

Previous Studies of D-Dimer in CAD

In ACS patients, the prognostic value of D-dimer levels for cardiovascular events remains controversial. Antithrombotic agents, such as heparin, which influence D-dimer levels, are routinely used in the acute phase of ACS. Thus, the differences in antithrombotic agents at the point of blood sampling may contribute to discordant results. Furthermore, the long-term predictive value of D-dimer for death has not been fully established among patients with stable CAD. The AtheroGene study, which included 1,057 patients angiographically confirmed as having CAD, showed an independent association between D-dimer levels and cardiovascular death. However, 30% of the study patients had ACS. Gong et al reported that D-dimer may be a use-
### Table 3. Multivariate Predictors of All-Cause and Cardiovascular Death Among Stable CAD Patients

| Variable | All-cause death |  | Cardiovascular death |  |
|----------|-----------------|---------------------|----------------------|---------------------|
|          | HR (95% CI)     | P value             | HR (95% CI)          | P value             |
| Age (per 10 years increment) | 1.44 (1.15–1.80) | 0.001               | 1.49 (1.16–1.81)     | 0.001               |
| Male     | 1.40 (1.01–1.94) | 0.04                | 1.35 (0.98–1.88)     | 0.07                |
|          | 0.70 (0.40–1.25) | 0.23                | 0.64 (0.36–1.13)     | 0.12                |
| Dyslipidemia | 0.70 (0.49–1.00) | 0.05                 | 0.72 (0.51–1.03)      | 0.07               |
| Diabetes | 1.30 (0.90–1.88) | 0.16               | 1.31 (0.91–1.89)      | 0.14               |
|          | 1.49 (0.89–2.51) | 0.13                | 1.56 (0.94–2.61)     | 0.09               |
| Paroxysmal or persistent AF | 1.43 (0.93–2.20) | 0.11         | 1.47 (0.96–2.27)      | 0.08               |
|          | 2.00 (1.14–3.48) | 0.02                | 2.04 (1.17–3.56)     | 0.01               |
| Hemoglobin (per 1 g/dL increment) | 0.93 (0.83–1.03) | 0.17                 | 0.92 (0.83–1.02)      | 0.13               |
|          | 0.88 (0.76–1.03) | 0.11                | 0.88 (0.76–1.03)     | 0.11               |
| hsCRP (per 10-fold increment) | 1.31 (0.92–1.86) | 0.14          | 1.30 (0.93–1.84)      | 0.13               |
|          | 1.48 (0.90–2.45) | 0.12                | 1.49 (0.92–2.41)     | 0.10               |
| D-dimer (per 10-fold increment) | 2.00 (1.32–3.05) | 0.001           | 2.39 (1.32–4.35)      | 0.004               |
| Tertile of D-dimer (μg/mL) |  |  |  |  |
| 1st (<0.32) | 1.61 (0.88–2.94) | 0.12               | 1.50 (0.51–4.37)     | 0.46               |
| 2nd (0.32–0.61) | 2.62 (1.48–4.64) | 0.0009            | 4.09 (1.56–10.7)     | 0.004               |
| 3rd (>0.61) | 0.86 (0.78–0.96) | 0.006            | 0.78 (0.67–0.91)      | 0.001               |
| Non-CKD  | 1.59 (1.09–2.32) | 0.02               | 2.73 (1.51–4.93)     | 0.0009              |
| CKD      | 1.30 (0.92–1.83) | 0.13               | 1.47 (0.91–2.38)     | 0.11               |
| eGFR (per 10mL/min/1.73 m² increment) | 0.80 (0.69–0.90) | 0.0007          | 0.80 (0.69–0.92)      | 0.001               |
| Non-CKD  | 0.64 (0.36–1.13) | 0.12               | 1.68 (0.61–4.65)     | 0.32               |
| CKD      | 1.68 (0.61–4.65) | 0.32               | 3.74 (0.62–22.7)     | 0.15               |
| LVEF (per 10% increment) | 0.79 (0.69–0.90) | 0.0007         | 0.80 (0.69–0.92)      | 0.001               |
| Non-CKD  | 0.64 (0.36–1.13) | 0.12               | 1.68 (0.61–4.65)     | 0.32               |
| CKD      | 1.68 (0.61–4.65) | 0.32               | 3.74 (0.62–22.7)     | 0.15               |

Multivariate model adjusted for all baseline variables with P<0.05 by univariate analysis. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

### Table 4. Adjusted Hazard Ratios of Combination of D-Dimer and eGFR for All-Cause and Cardiovascular Death

| Variable | All-cause death |  | Cardiovascular death |  |
|----------|-----------------|---------------------|----------------------|---------------------|
|          | HR (95% CI)     | P value             | HR (95% CI)          | P value             |
| Age (per 10 years increment) | 1.45 (1.15–1.81) | 0.001               | 1.35 (0.97–1.87)     | 0.07               |
| Male     | 0.64 (0.36–1.13) | 0.12               | 1.68 (0.61–4.65)     | 0.32               |
| Dyslipidemia | 0.72 (0.51–1.03) | 0.07               | 1.59 (1.09–2.32)     | 0.02               |
| Diabetes | 1.31 (0.91–1.89) | 0.14               | 2.06 (1.18–3.60)     | 0.07               |
| Paroxysmal or persistent AF | 1.48 (0.96–2.27) | 0.08               | 1.58 (0.94–2.63)     | 0.08               |
| Hemoglobin (per 1 g/dL increment) | 0.92 (0.83–1.02) | 0.13               | 0.88 (0.76–1.03)     | 0.11               |
| hsCRP (per 10-fold increment) | 1.30 (0.92–1.83) | 0.13               | 1.47 (0.91–2.38)     | 0.11               |

Multivariate model adjusted for all baseline variables with P<0.05 in the univariate analysis. Abbreviations as in Tables 1,3.
Mechanisms of Increased D-Dimer Levels

D-dimer reflects fibrin turnover. Because patients with evident venous thrombotic conditions were excluded, the median plasma D-dimer value in the present study was 0.43 μg/mL, which was lower than the cutoff value of 1.0 μg/mL that is recommended to rule out venous thrombosis and pulmonary embolism. Mechanisms for the association between modest increases in D-dimer level and long-term death in stable CAD patients remain unclear. Cardiovascular death is mostly attributed to the development of acute thrombosis at the site of a ruptured atherosclerotic plaque. The independent association between cardiovascular death and D-dimer level in the present study suggested that a hypercoagulability state may be involved in this process. Also, previous studies have suggested that endothelial dysfunction is a possible mechanism by which D-dimer levels may contribute to cardiovascular risk and death. A procoagulant state may be a cause or consequence of underlying endothelial dysfunction that facilitates atherosclerotic disease. Plethysmography, flow-mediated dilation, and biomarkers such as asymmetric dimethylarginine, soluble vascular adhesion molecule-1, or von Willebrand factor are used to evaluate endothelial function, but they were not performed in the present study. Further studies are needed to clarify this issue. Furthermore, higher D-dimer levels were significantly associated with a higher prevalence of multivessel CAD in the present study, which was consistent with previous studies. Thus, higher D-dimer levels might reflect extensive atherosclerosis, resulting in poor prognosis.

Study Limitations

First, this study was conducted at a single institution. Larger, multicenter studies are warranted to corroborate our findings. Second, we only measured D-dimer levels at the time of enrollment. Therefore, we did not evaluate whether D-dimer levels could function as a monitoring marker and whether improvements in this biomarker would affect the predictor of major adverse cardiovascular events in patients with stable CAD. The mean follow-up period of their study was shorter than in our study (18 vs. 73 month, respectively). They also could not evaluate the association of D-dimer with death because of the small number of deaths. Thus, we only focused on stable CAD patients and demonstrated, for the first time, the independent association of D-dimer levels with long-term all-cause and cardiovascular death in stable CAD patients.

### Table 5. Discrimination and Reclassification of the Combination of D-Dimer and eGFR for All-Cause and Cardiovascular Death

|                         | C-index | P value | NRI   | P value | IDI   | P value |
|-------------------------|---------|---------|-------|---------|-------|---------|
| **All-cause death**     |         |         |       |         |       |         |
| Established risk factor model | 0.707   | Ref.    | Ref.  | Ref.    |       | Ref.    |
| Established risk factor model+eGFR | 0.733   | 0.456   | 0.313 | 0.0004  | 0.021 | <0.0001 |
| Established risk factor model+D-dimer | 0.745   | 0.271   | 0.4380| <0.0001 | 0.017 | 0.0007 |
| Established risk factor model+eGFR+D-dimer | 0.759   | 0.123   | 0.440 | <0.0001 | 0.031 | <0.0001 |
| Established risk factor model+eGFR vs. Established risk factor model+D-dimer | 0.026*  | 0.428   | 0.371 | <0.0001 | 0.011 | 0.02   |
| Established risk factor model+eGFR+D-dimer vs. Established risk factor model+D-dimer | 0.014*  | 0.654   | 0.275 | 0.002   | 0.014 | 0.002  |
| **Cardiovascular death**|         |         |       |         |       |         |
| Established risk factor model | 0.750   | Ref.    | Ref.  | Ref.    |       | Ref.    |
| Established risk factor model+eGFR | 0.802   | 0.218   | 0.566 | <0.0001 | 0.038 | <0.0001 |
| Established risk factor model+D-dimer | 0.799   | 0.228   | 0.780 | <0.0001 | 0.022 | 0.0005 |
| Established risk factor model+eGFR+D-dimer | 0.830   | 0.043   | 0.768 | <0.0001 | 0.052 | <0.0001 |
| Established risk factor model+eGFR+D-dimer vs. Established risk factor model+D-dimer | 0.028*  | 0.455   | 0.627 | <0.0001 | 0.013 | 0.03   |
| Established risk factor model+eGFR+D-dimer vs. Established risk factor model+D-dimer | 0.031*  | 0.402   | 0.519 | <0.0001 | 0.030 | 0.0002 |

*Estimated differences between 2 groups. Established risk factors included age, sex, hypertension, dyslipidemia, diabetes, smoking status, paroxysmal or persistent AF, previous MI, and previous coronary revascularization. IDI, integrated discrimination improvement; NRI, net reclassification improvement. Other abbreviations as in Table 1.
study outcomes. In addition, therapies and risk factors that may have changed during a mean follow-up period of 73 months were not considered. Such analysis is necessary in subsequent studies. Third, it is important to identify patients who would benefit from more aggressive and focalized treatment among patients with CAD. Considering our results, CAD patients with the highest coagulation status may benefit greatly from anticoagulant use. In addition, those who have the highest coagulation status may benefit from statin use, regardless of dyslipidemia, because of the drug’s pleiotropic effects, including improvement in endothelial function. Further studies will be necessary to determine whether a treatment policy based on this biomarker’s levels would reduce the risk of death among stable CAD patients. Finally, treatments were not randomized in the present study, so it was difficult to evaluate their effects on mortality rates. Thus, we did not evaluate drug treatments using Cox multivariate analyses. In the present study, patients with higher D-dimer levels were significantly associated with less use of statins. In addition to infrequent antiplatelet therapy and statin use, patients who died used angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers and β-blockers more frequently than survivors. Thus, differences in medications may have potential confounding effects on our results. However, when we entered these medications into our Cox multivariate analyses, both D-dimer and eGFR were still independent and significant predictors of all-cause and cardiovascular death. Thus, we believe that the medications did not significantly contribute to our results.

Conclusions

Combining D-dimer and eGFR values, which are independent predictors of death, may be useful for predicting long-term outcomes of patients with stable CAD.

Funders

None.

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