Sudden Cardiac Death in End-Stage Renal Disease Patients
A 5-Year Prospective Analysis

Angela Yee-Moon Wang, Christopher Wai-Kei Lam, Iris Hiu-Shuen Chan, Mei Wang, Siu-Fai Lui, John E. Sanderson

Abstract—End-stage renal disease patients experience a high incidence of sudden cardiac death. We performed a 5-year prospective study in 230 end-stage renal disease patients, aiming to determine the role of echocardiography and the additional value of serum biomarkers in predicting sudden cardiac death. During follow-up, 24% of all deaths were attributed to sudden cardiac death. In the multivariable Cox regression analysis considering clinical, biochemical, dialysis, and echocardiographic parameters, left ventricular systolic dysfunction emerged as the most significant predictor of sudden cardiac death, followed by a high systolic and a low diastolic blood pressure. An ejection fraction cutoff \( \leq 48.0\% \) is associated with a specificity of 78.6% and a sensitivity of 57.7% in predicting sudden cardiac death. In biomarker-based multivariable Cox regression analysis, N-terminal probrain natriuretic peptide displays an independent association with sudden cardiac death and is more significantly associated with sudden cardiac death than cardiac troponin T. In the combined echocardiography and biomarker-based multivariable Cox regression model, N-terminal probrain natriuretic peptide loses significance to left ventricular ejection fraction, whereas cardiac troponin T retains a significant association with sudden cardiac death independent of echocardiographic parameters. In conclusion, systolic dysfunction is the most significant predictor of sudden cardiac death followed by a high systolic and a low diastolic blood pressure. Our data suggest additional value in measuring cardiac troponin T for sudden cardiac death risk stratification. N-terminal probrain natriuretic peptide may be used in place of echocardiography to identify patients at risk of sudden cardiac death but had no added value over echocardiography in predicting sudden cardiac death. (Hypertension. 2010;56:210-216.)

Key Words: sudden cardiac death ■ cardiac troponin T ■ N-terminal probrain natriuretic peptide ■ end-stage renal disease ■ peritoneal dialysis ■ echocardiography ■ systolic dysfunction

Dialysis patients are at a heightened risk of developing cardiovascular mortality. According to recent data from the US Renal Data System, cardiac disease is the leading cause of mortality, accounting for 43% of all-cause mortality in patients receiving hemodialysis or peritoneal dialysis (PD).\(^1\) The incidence of death attributable to cardiac arrest/cause unknown or arrhythmia is high in end-stage renal disease (ESRD) patients, accounting for \( \sim 25\% \) of all-cause mortality. These rates are similar in hemodialysis and PD patients.\(^1\) However, there have been very few prospective data on risk factors associated with sudden cardiac death (SCD) in ESRD patients and virtually none in patients receiving long-term PD.

Data from the general population cannot simply be extrapolated to the ESRD population, because ESRD patients are subjected not only to traditional Framingham risk factors but also, more importantly, kidney disease-related risk factors, such as inflammation, increased calcium×phosphorus product, uremic toxins, anemia, and fluid overload. The risk of cardiovascular mortality is \( \geq 10\% \) to 100-fold higher in the ESRD population compared with the age-, sex-, and race-matched general population.\(^2\) Other than being at risk for accelerated atherosclerosis, ESRD patients show a very high prevalence of vascular\(^3,4\) and valvular calcifications,\(^5\) and these have been shown to be associated with increased arterial stiffness\(^6\) and adverse outcomes.\(^7,9\) ESRD patients also have very high prevalence of left ventricular (LV) hypertrophy\(^10,11\) with associated fibrosis, and that may predispose to inadequate coronary reserve and cardiac ischemia, leading to an increased risk of heart failure.\(^12\) Inflammation and sympathetic overactivity may also act as potential triggers for arrhythmias in patients with diseased myocardium, and they may result in SCD.\(^13\)

Given this background, we first aimed to test the hypothesis that specific echocardiographic parameters, including LV...
mass index and ejection fraction, may be useful in predicting SCD in ESRD patients receiving PD treatment and, if so, the best cutoff of these parameters in predicting SCD. Second, given that echocardiography is not always readily available in most dialysis centers, we aimed to test whether serum biomarkers may be used in place of echocardiography to identify ESRD patients at risk of SCD. Third, we aimed to examine the additional role, if any, of a panel of serum biomarkers, including C-reactive protein (CRP), interleukin 6 (IL-6), fetuin-A, cardiac troponin T (cTnT), N-terminal probrain natriuretic peptide (NT-pro-BNP), and myeloperoxidase (MPO), to echocardiography in predicting SCD in these patients.

Methods

Study Design
This is a 5-year prospective observational cohort study performed at a single regional dialysis center in Hong Kong between 1999 and 2005. The study protocol was approved by the institutional research ethics committee of the Chinese University of Hong Kong. All of the patients provided informed consent before enrollment into the study.

Study Subjects
ESRD patients who have been started on long-term continuous PD therapy for ≥3 months and did not fulfil any of the exclusion criteria were considered eligible for study inclusion. Exclusion criteria included patients with underlying malignancy, chronic obstructive airways disease, chronic rheumatic heart disease, or congenital heart disease, as well as patients who refused to provide study consent or patients with incomplete data. On the basis of the inclusion and exclusion criteria, 117 men and 113 women were recruited, and they represented 85% of the entire PD population in the center. All of the patients were dialyzed using conventional lactate-buffered, glucose-based PD solutions.

Assessments

Echocardiography
At study baseline, 2D echocardiography was carried out in all of the patients lying in the left decubitus position using a GE-VingMed System 5 echocardiographic machine (GE-VingMed Sound AB) with a 3.3-MHz multiphase array probe by a single experienced cardiologist blinded to all of the clinical details of patients. All of the echocardiographic data were recorded according to the guidelines of the American Society of Echocardiography.14,15

Biochemical Measurements
A 20-mL fasting venous blood sample was collected at study baseline for the measurement of cTnT, NT-pro-BNP, high-sensitivity CRP (hs-CRP), IL-6, fetuin-A, MPO, albumin, fasting lipids, renal function, bone profile, intact parathyroid hormone, and hemoglobin. Detailed methods for the different biochemical assays are provided in the online Data Supplement (please see http://hyper.ahajournals.org).

Measurements of Indices of Dialysis Adequacy
At study entry, 24-hour urine sample and dialysate were also collected for measurement of total weekly urea and creatinine clearances using standard methods.16 Residual glomerular filtration rate was estimated as the average of 24-hour urine urea and creatinine clearances.17

Data Collection
At study entry, a thorough medical history was taken from all of the study patients. Details on data collection are provided in the online Data Supplement.

Follow-Up and Outcome Measure

The cohort was assembled purposely to study the outcome of SCD, which was defined “a priori” as sudden unexpected natural death within 1 hour from the symptom onset and without any immediate previous condition that would appear fatal.18,19 Given the sudden and unexpected nature of death, there is usually not enough time to allow extensive investigations to be performed before death. If investigations were performed and the cause of death identified, the deaths were not considered as SCD. For instance, in patients who developed acute myocardial infarction, aortic dissection, acute pulmonary embolism, or some other acute infections and then developed SCD shortly or immediately after the acute event, these deaths were not considered as SCDs because there were attributable causes. Death preceded by an arrhythmic event was classified as attributed to malignant arrhythmia and not as SCD. Deaths occurring after termination of dialysis were not regarded as unexpected and, thus, not as SCD. All of the deaths were accurately recorded with the exact cause of death provided by the attending physician. For out-of-hospital deaths, family members were interviewed by telephone to ascertain the circumstances surrounding the death. All of the patients were followed up prospectively for 5 years from the day of baseline assessment at study entry, until death, or until they underwent kidney transplant. No patient was lost to follow-up.

Statistical Analysis
Baseline characteristics were presented as mean±SD or median (interquartile range) for continuous data where appropriate or number (%) for categorical data. Kaplan-Meier survival analysis was used to estimate the cumulative SCD event-free survival probability in relation to tertiles of cTnT and NT-pro-BNP. Patients who underwent kidney transplantation during follow-up were censored at the time of transplantation. Patients who died from other cardiac causes or noncardiovascular causes were also censored at the time of death. Relative risks and 95% CI from the Cox proportional-hazards regression models were used to evaluate the associations of different risk factors to SCD. To test the 3 hypotheses, separate multivariable Cox regression analyses for SCD were performed using a backward elimination strategy considering variables with P<0.2 on univariate Cox regression analysis. Details on multivariable Cox regression analysis are provided in the online Data Supplement. Although the study cohort is relatively large, the number of SCDs remained fairly low. We adjusted each regression coefficient in the final multivariable Cox regression model with a shrinkage factor to correct for overfitting.20 Details on how the shrinkage factor was derived are shown in the online Data Supplement. A P value of <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS version 16.0 (SPSS, Inc.).

Results
The baseline characteristics of the study population are shown in Table 1. Background causes of ESRD included 74 cases of chronic glomerulonephritis (32.2%), 55 cases of diabetic nephropathy (23.9%), 31 cases of hypertensive nephrosclerosis (13.5%), 12 cases of polycystic kidney disease (5.2%), 13 cases of obstructive uropathy (5.7%), 6 cases of tubulointerstitial nephritis (2.6%), and no cause identified in 39 cases (17.0%). During the 5-year follow-up, a total of 115 deaths occurred, of which 28 deaths were attributed to SCD, and 87 deaths were attributed to non-SCD causes.

Table 2 presents the univariate Cox regression analysis of factors predicting SCD. Of the serum biomarkers, only cTnT and NT-pro-BNP are significantly associated with SCD, and fetuin-A shows marginal association (P<0.2) on univariate analysis. The associations of hs-CRP, IL-6, and MPO with SCD are all highly insignificant on univariate analysis (P>0.2), and, thus, they are not further considered in multivariable Cox regression analysis. We stratified patients by
tertiles of NT-pro-BNP and cTnT. Figure A and B show the SCD event-free survival probability of patients stratified by tertiles of NT-pro-BNP and cTnT, respectively. A significant graded increase in the risk of developing SCD is observed across the 3 tertiles of increasing NT-pro-BNP (P<0.001) and cTnT (P=0.001). We compared the strength of association between cTnT and NT-pro-BNP with SCD in Table S1 (please see the online Data Supplement). NT-pro-BNP shows a stronger association with SCD than cTnT. NT-pro-BNP retains significant association with SCD when adjusting for cTnT, whereas cTnT loses significance when adjusting for NT-pro-BNP.

Table 3 presents 3 separate multivariable Cox regression models for SCD. Model 1 considers clinical, biochemical, and dialysis parameters, as well echocardiographic parameters with P<0.2 on a univariate analysis (echocardiography-based model). Model 2 includes the same clinical, biochemical, and dialysis parameters, as well as serum biomarkers with P<0.2 on univariate analysis but not echocardiographic parameters (biomarker-based model). Because hs-CRP, IL-6, and MPO are all highly insignificant in the univariate analysis, only cTnT, NT-pro-BNP, and fetuin-A are considered in the multivariable Cox regression analysis. Model 3 includes both echocardiographic parameters and serum biomarkers, in addition to clinical, biochemical, and dialysis parameters, with P<0.2 on univariate analysis (combined echocardiography and biomarker-based model). In the echocardiography-based Cox model, LV systolic dysfunction is the most significant predictor of SCD, followed by a high systolic blood pressure and a low diastolic blood pressure. Using the receiver-operator characteristics curve analysis, the best cutoff of LV ejection fraction in predicting SCD is 39.9% and is associated with a specificity of 78.6% (95% CI: 72.2% to 84.1%) and a sensitivity of 57.7% (95% CI: 36.9% to 76.6%). In the biomarker-based Cox model, NT-pro-BNP is independently predictive of SCD and is more significant than cTnT in predicting risk of SCD. In the combined echocardiography and biomarker-based model, NT-pro-BNP does not retain independent significance in the model.
whereas LV systolic dysfunction and cTnT retain independent, significant predictive values for SCD.

Discussion

In this prospective cohort study of Chinese ESRD patients receiving chronic PD treatment, we observed a high incidence of SCD over a 5-year longitudinal follow-up. Twenty-four percent of all-cause mortality was attributed to SCD. This incidence is almost identical to that reported in the US Renal Data System database, in which 25% of all-cause death among PD patients and 27% of all-cause death among hemodialysis patients in the United States are attributed to cardiac arrest/cause unknown.1 This observation is not surprising, given that PD patients are similarly subjected to kidney disease or uremia-related risk factors as in hemodialysis patients.

Our results show that systolic dysfunction is the most significant predictor of SCD, followed by a high systolic and a low diastolic blood pressure. This is in keeping with data from the general population showing that reduced ventricular function was the strongest predictor for SCD.21,22 Our study shows for the first time that an ejection fraction ≤48% is the best cutoff threshold in predicting an increased risk of SCD in ESRD patients with ≥80% specificity. Poor systolic function may predispose to heart failure and increase the risk of electric instability and ventricular arrhythmia via neurohumoral/sympathetic activation.23,24

The association among background atherosclerotic vascular disease, valvular calcification, and SCD in our ESRD patients is consistent with observations in the general population that obstructive coronary artery disease with resulting myocardial ischemia was the most common triggering factor for SCD.25 Previous studies show that valvular calcification is a marker of atherosclerosis26 and predicts cardiovascular death9 in ESRD patients. There is also evidence that valvular calcification is associated with vascular calcification27 and increased arterial stiffening and may, thus, increase LV hypertrophy.28,29 The diseased myocardium secondary to coronary ischemia, together with myocardial fibrosis and/or hypertrophy, provide additional substrate for an increased electric instability13 and may, thus, contribute to an increased risk of SCD in uremic patients. In this study, systolic hypertension and a low diastolic blood pressure, reflecting increased arterial stiffening or reduced arterial distensibility, both independently predict an increased risk of SCD. Previous studies also reported the importance of blood pressure control in dialysis patients.30–32 It is well recognized that systolic hypertension and increased arterial stiffness contribute to LV hypertrophy in ESRD patients.29 Our results showed that LV hypertrophy was a significant predictor of SCD but lost its significance to systolic hypertension and low diastolic blood pressure in multivariable Cox regression models. Of importance, systolic hypertension and low diastolic blood pressure consistently retained independent significance in all 3 of the multivariable Cox regression models for SCD. These observations clearly confirm the importance of blood pressure control in ESRD patients and suggest that systolic hypertension and arterial stiffening may act as potential triggers in the presence of an abnormal myocardium and predispose to arrhythmias and, consequently, SCD.

Previous studies demonstrated the prognostic importance of cTnT in ESRD patients.33–35 cTnT is a highly sensitive marker of myocardial damage. There is pathological evidence that elevated cTnT is associated with subclinical myocardial necrosis or microinfarct.36,37 In uremic cardiac hypertrophy, myocardial capillary growth does not keep pace with cardiomyocyte hypertrophy, resulting in cardiomyocyte/capillary mismatch, and reduces ischemic tolerance of the heart.38 This may further increase the risk of subclinical ischemic insults to the myocardium and amplify the leakage of cardiac troponins across the plasma membrane of myocardial cells into the circulation. In this study, cTnT retained a significant association with SCD independent of echocardiographic parameters. This suggests that measurement of cTnT to stratify SCD risk in ESRD patients may give additional value. It is likely that cTnT reflects subclinical myocardial necrosis or injury that is not captured by standard echocardiographic parameters LV mass and ejection fraction, although they are correlated with cTnT.35 Our results are in keeping with a study in hemodialysis patients showing that cTnT strongly correlated...
with all-cause mortality even after adjusting for LV systolic function.\textsuperscript{39}

On the other hand, NT-pro-BNP independently predicts SCD in a biomarker-based model but not in a combined echocardiography and biomarker-based model. Brain natriuretic peptide is a peptide hormone released primarily by the ventricular myocytes in response to myocyte stretch, such as increased cardiac filling pressure.\textsuperscript{40} Population studies have suggested that plasma brain natriuretic peptide and NT-pro-BNP levels are useful screening tests for heart failure\textsuperscript{41} and systolic dysfunction.\textsuperscript{42} NT-pro-BNP has been shown to strongly correlate with LV systolic dysfunction and is more strongly associated with mortality than cTnT, suggesting that volume overload may play a role in predicting outcome.\textsuperscript{39} This is in keeping with our current observation that NT-pro-BNP had a stronger association with SCD than cTnT. There is increasing evidence that brain natriuretic peptide and NT-pro-BNP are powerful prognostic tools in the ESRD population.\textsuperscript{43,44} In PD patients, NT-pro-BNP is associated with LV hypertrophy and systolic dysfunction independent of residual renal function.\textsuperscript{44} In a more recent study, elevated NT-pro-BNP has been demonstrated to be a useful biomarker in predicting severe LV hypertrophy and ruling out systolic dysfunction in the PD patients.\textsuperscript{45} The finding that NT-pro-BNP predicts SCD in a biomarker-based model but loses significance to LV ejection fraction in a combined echocardiography and biomarker-based model suggests that its association with SCD is likely mediated via its close relations with systolic dysfunction. These findings on cTnT and NT-pro-BNP have several important novel clinical implications in that NT-pro-BNP measurement may be used in place of echocardiography to identify ESRD patients at risk of SCD but has no added value over echocardiography in predicting risk of SCD. If echocardiography is not available, then NT-pro-BNP appears to be the most useful serum biomarker in predicting SCD in ESRD patients, because it displays independent predictive value for SCD beyond the standard echocardiographic parameters.

Contrary to the Choices for Healthy Outcomes in Caring for ESRD Study showing how inflammation, such as CRP and IL-6, increased the risk of SCD,\textsuperscript{46} we found no significant association between a single time point of measured serum inflammatory protein, including CRP, IL-6, MPO, or fetuin-A, and SCD in our patients. It is not clear whether this difference may be explained by the fact that our study includes prevalent PD patients in contrast to the Choices for Healthy Outcomes in Caring for ESRD Study, which included incident and predominantly hemodialysis patients. There is some suggestion that hemodialysis may induce CRP more than PD,\textsuperscript{47,48} but this will require confirmation in a larger prospective controlled study. Unlike our study, the Choices for Healthy Outcomes in Caring for ESRD Study\textsuperscript{46} did not include any cTnT, NT-pro-BNP, or echocardiographic data.

The strengths of our study include that it is so far the longest prospective follow-up (5 years) study that evaluated

<table>
<thead>
<tr>
<th>Model and Variable</th>
<th>Unit Increase</th>
<th>Shrinkage Corrected HR</th>
<th>Shrinkage Corrected 95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Echocardiography-based model</td>
<td>1 mm Hg</td>
<td>0.04</td>
<td>1.01 to 1.07</td>
<td>0.0057</td>
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<tr>
<td>Diastolic blood pressure</td>
<td>1 mm Hg</td>
<td>0.92</td>
<td>0.87 to 0.97</td>
<td>0.0044</td>
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<td>LV ejection fraction</td>
<td>1%</td>
<td>0.93</td>
<td>0.89 to 0.97</td>
<td>0.0012</td>
</tr>
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<td>0.45</td>
<td>0.19 to 1.11</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>0.54</td>
<td>0.22 to 1.28</td>
<td>0.16</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td>1000 pg/mL</td>
<td>1.05</td>
<td>1.01 to 1.08</td>
<td>0.0044</td>
</tr>
<tr>
<td>cTnT</td>
<td>0.1 μg/L</td>
<td>1.14</td>
<td>0.99 to 1.30</td>
<td>0.061</td>
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<tr>
<td>Combined echocardiography- and biomarker-based model</td>
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<td>1.02 to 1.08</td>
<td>0.0031</td>
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<tr>
<td>Diastolic blood pressure</td>
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<td>0.87 to 0.97</td>
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<tr>
<td>Erythropoietin use</td>
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<td>0.18 to 1.06</td>
<td>0.066</td>
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<tr>
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<td>0.20 to 1.15</td>
<td>0.10</td>
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<tr>
<td>cTnT</td>
<td>0.1 μg/L</td>
<td>1.14</td>
<td>1.01 to 1.31</td>
<td>0.031</td>
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<tr>
<td>Valvular calcification</td>
<td>...</td>
<td>1.90</td>
<td>0.83 to 4.32</td>
<td>0.13</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>1%</td>
<td>0.94</td>
<td>0.89 to 0.98</td>
<td>0.004</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio.

*All of the models considered the same clinical, biochemical, and dialysis parameters with P<0.2 on univariate analysis.
SCD in ESRD patients. The outcome of SCD was defined as a priori using strict standard criteria. All of the patients had detailed comorbid data, echocardiographic examination together with a comprehensive panel of serum inflammatory proteins, cardiac biomarkers including cTnT and NT-pro-BNP, as well as indices of dialysis adequacy at baseline before entering a 5-year prospective follow-up period. There was no patient loss to follow-up. The incidence of SCD in our population is very similar to that reported in the US Renal Data System, and, thus, the results should be representative of the dialysis population at large. However, there are also limitations. First, the study was performed in prevalent PD patients and may introduce survival bias. Second, although the study cohort was followed for a fairly long period, the total number of SCDs remains quite low, because SCD accounts for 24% of total mortality. We, therefore, adjusted the analysis by a “shrinkage factor,” making the analysis more conservative. Our observations will require confirmation in larger studies. Third, we evaluated the association of a single time point measurement of different parameters with SCD and did not take into account changes with time on dialysis. However, this reproduces the typical situation of daily clinical practice and is also the primary aim of our study, that is, to determine how the different parameters measured at a 1-off time point may be used to identify patients at risk of SCD years later.

Perspectives
There are only scant data on risk factors predicting SCD in the ESRD population. In this 5-year prospective follow-up study, we evaluated how echocardiography, serum biomarkers, and other clinical parameters assessed at a 1-off time point may be used to identify ESRD patients at risk of SCD some years later. Our results demonstrate the importance of systolic dysfunction (with the best ejection fraction cutoff ≤48%), a high systolic blood pressure, and a low diastolic blood pressure in predicting SCD in ESRD patients. Our data suggest additional value in measuring cTnT, because it gives independent predictive value for SCD beyond echocardiographic parameters. NT-pro-BNP may be used in place of echocardiography to predict SCD but has no additional role if echocardiography is available. These observations require confirmation in larger ESRD cohorts.

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Disclosures
None.

References


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Sudden Cardiac Death in End-Stage Renal Disease Patients: A 5-year Prospective Analysis

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Method

Assessments

Data Collection

Clinical and demographic data including the presence of diabetes, smoking status, details of any previous history of angina, myocardial infarction with or without percutaneous coronary intervention or coronary artery bypass grafting, previous stroke or transient ischemic attacks, intermittent claudication or other symptoms suggestive of peripheral vascular disease with or without history of amputation or revascularization and use of different anti-hypertensive medications and erythropoietin were recorded. With a mercury sphygmomanometer, systolic and diastolic blood pressure were measured once on every follow-up visit after patient was rested for 15 minutes on either arm at 8 week intervals for 12 months preceding study entry and were then averaged to give the final systolic and diastolic blood pressure.

Biochemical measurements

cTnT and NT-pro-BNP were measured by electrochemiluminescence immunoassays on the Elecsys 2010 analyser (Roche Diagnostics Corp, Indianapolis, IN, USA) with a detection limit of 0.01 µg/L and 5 pg/mL, respectively. For samples with NT-pro-BNP concentrations above the measuring range 35,000 pg/mL, the final concentrations would be taken as 35,000 pg/mL. CRP and albumin were measured using the Tina-quant CRP latex ultra-sensitive assay (detection limit of 0.01mg/L) and the bromcresol purple method, respectively, on the Roche modular analyzer (Roche Diagnostics, USA). IL-6 was measured using the enzyme-linked immunosorbent assay (ELISA) (BioSource International Inc, Camarillo, CA, USA) (detection limit of 2 pg/mL). Serum fetuin-A was determined using a human fetuin-A ELISA assay kit (Epitope Diagnostics, San Diego, USA). Plasma MPO was measured using a sandwich ELISA kit (Immunodiagnostik AG, Bensheim, Germany) with a detection limit of 1.6 µg/L. Calcium and phosphorus concentrations were measured using dye-binding methods on the Dimension AR automatic analyzer (Du Pont Co, Wilmington, DE, USA). iPTH was determined by chemiluminescence immunoassay on the Immulite analyzer (Diagnostic Products Corp, Los Angeles, CA, USA). Total cholesterol and triglyceride were assayed enzymatically (Hitachi 911 analyser, Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

Multivariable Cox regression analysis

In echocardiography-based model, we considered clinical, biochemical, dialysis and echocardiography parameters but not serum biomarkers. In biomarker-based model, clinical, biochemical, dialysis parameters and serum biomarkers were included but not echocardiographic parameters. In combined echocardiography and biomarker-based model, clinical, biochemical, dialysis, echocardiography parameters and serum biomarkers were considered.
**Shrinkage factor**

In brief, the shrinkage factor was derived using the formula: (overall chi square of the model to the power 2 – the number of parameters in the model) divided by overall chi square of the model to the power 2. Each regression coefficient is then multiplied by the shrinkage factor. The standard error (SE) is considered unchanged. The shrinkage corrected hazard ratios can then be calculated from the formula: hazard ratios = exp \( \text{shrinkage corrected coefficient} \). The corresponding 95% confidence intervals can be calculated by the formula: 95% CI = exp \( \text{shrinkage corrected coefficient} \) ± 1.96*SE. We calculated the P-value from the Wald statistics which produced a Chi-Square distribution with 1 degree of freedom. The exact P value is the P-value corresponding to a given Chi-Square value.
Table S1. Cox regression analysis of SCD in relation to tertiles of N-terminal pro-brain natriuretic peptide and cardiac troponin T considered separately and together.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unadjusted HR (95% CI)</th>
<th>P</th>
<th>Adjusted HR (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-pro-BNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower tertile</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Middle tertile</td>
<td>6.37 (1.41 – 28.78)</td>
<td>0.016</td>
<td>5.06 (1.09 – 23.51)</td>
<td>0.038</td>
</tr>
<tr>
<td>Upper tertile</td>
<td>11.94 (2.72 – 52.43)</td>
<td>0.001</td>
<td>7.54 (1.55 – 36.69)</td>
<td>0.012</td>
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<tr>
<td></td>
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<td>Chi-square = 8.93, P=0.012</td>
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<tr>
<td>cTnT</td>
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<tr>
<td>Lower tertile</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Middle tertile</td>
<td>2.77 (0.85 – 8.99)</td>
<td>0.09</td>
<td>1.91 (0.58 – 6.32)</td>
<td>0.29</td>
</tr>
<tr>
<td>Upper tertile</td>
<td>5.67 (1.87 – 17.14)</td>
<td>0.002</td>
<td>2.58 (0.78 – 8.57)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chi-square = 2.71, P=0.26</td>
<td></td>
</tr>
</tbody>
</table>

NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; cTnT, cardiac troponin T; HR, hazard ratios; CI, confidence intervals.

*The Cox regression model of NT-pro-BNP in relation to SCD was adjusted for cTnT. The Cox regression model of cTnT in relation to SCD was adjusted for NT-pro-BNP.

The likelihood ratio chi-square statistic was used for model comparisons.

For NT-pro-BNP: Lower tertile NT-pro-BNP < 2665 pg/mL (n=77); middle tertile ≥ 2666 – 11893 pg/mL (n=77); upper tertile ≥ 11894 pg/mL (n=76).

For cTnT: Lower tertile cTnT ≤ 0.01 µg/L (n=81); middle tertile > 0.01 – 0.099 µg/L (n=70); upper tertile ≥ 0.1 µg/L (n=79).