Prognostic Value of High-Sensitivity Versus Conventional Cardiac Troponin T Assays Among Patients With Type 2 Diabetes Mellitus Undergoing Maintenance Hemodialysis

Till Keller, Christoph Wanner, Vera Krane, Daniel Kraus, Bernd Genser, Hubert Scharnagl, Winfried März, and Christiane Drechsler

Background: Mortality is high among patients undergoing hemodialysis for whom cardiac troponin concentration is a strong predictor of outcome. Modern troponin assays allow measurement of very low concentrations.

Study Design: Using data from a randomized controlled trial, a cohort analysis to evaluate the prognostic value of very low cardiac troponin T (TnT) concentrations.

Setting & Participants: 1,255 patients with end-stage renal disease and type 2 diabetes mellitus undergoing maintenance hemodialysis from the German Diabetes and Dialysis Study (4D) who had a median follow-up of 4 years.

Index Test, Reference Test, and Outcome: Cardiac TnT was measured using a high-sensitivity assay (hs-TnT) and a conventional assay (conventional TnT) in a subpopulation (n = 1,034) with valid measurements for both assays. Outcome measures were all-cause mortality and a composite cardiovascular end point including cardiac death, myocardial infarction, or stroke.

Results: Among the 1,034 study participants, 505 died and 377 had a cardiovascular event. Both hs-TnT and conventional TnT concentrations were associated with mortality and cardiovascular events in models adjusted for cardiovascular risk factors and dialysis-associated variables. 455 (44%) patients with very low TnT concentrations (hs-TNT < 50 ng/L) would have been classified as normal by the conventional TnT assay. Among these patients, hs-TnT concentrations were also associated with mortality.

Limitations: The study of patients with type 2 diabetes may limit generalizability. These findings have not been externally validated.

Conclusions: In patients with type 2 diabetes mellitus receiving hemodialysis, cardiac TnT is associated with long-term mortality and cardiovascular outcomes. Concentrations of TnT not measurable with acceptable precision using a conventional TnT assay were associated with a poor prognosis when measured using a high-sensitivity assay.

Complete author and article information provided before references.

Correspondence to T. Keller (keller@chestpain.de)

Am J Kidney Dis. 71(6): 822-830. Published online January 6, 2018.

doi: 10.1053/j.ajkd.2017.10.016

© 2017 by the National Kidney Foundation, Inc.

Patients with end-stage renal disease (ESRD) who undergo hemodialysis have the highest observed mortality among patients with chronic kidney disease.[1,2] Type 2 diabetes, one of the most common diagnoses among hemodialysis patients, may aggravate this poor survival,[3] and cardiovascular events account for a large proportion of the high mortality in patients receiving hemodialysis.[4] Concentrations of cardiac troponin I and T (TnT) as measured using conventional assays, with elevated concentrations representing myocardial necrosis and potentially recurrent myocardial ischemia,[5] are well-known biomarkers to predict mortality and cardiovascular events in patients receiving dialysis.[6-8] Thus, cardiac troponin concentrations could be used for risk stratification in dialysis patients.[9]

One major use of cardiac troponin determination is the diagnosis of acute myocardial infarction. Based on the revised third definition of myocardial infarction[10] with strict recommendations on test precision, the assay sensitivity of cardiac troponin I and TnT has improved substantially during the past few years. This led to a lower limit of detection of these assays, allowing determination of very low troponin concentrations. Clinical application of these high-sensitivity assays with higher test precision at the diagnostic threshold concentration, representing a reference population's 99th percentile, facilitates early diagnosis of myocardial infarction.[11-13] Recently, the first high-sensitivity assay for TnT has been approved by the US Food and Drug Administration for use in the United States.[14] Currently, there is not much robust information available for the prognostic relevance of this high-sensitivity assay for TnT in patients receiving dialysis. Elimination of circulating cardiac troponin, especially TnT, is thought to rely at least partly on kidney function.[15,16] In the era of high-sensitivity troponin assays, whether precise measurement of very low concentrations of cardiac troponin in patients with ESRD represents cardiovascular risk or just accumulation due to reduced clearance is still unclear.

The aim of the present study was to explore the association of low cardiac TnT concentrations with outcomes if measured using a high-sensitivity assay compared to a conventional assay in the high-risk group of patients with ESRD with type 2 diabetes mellitus undergoing hemodialysis.

Methods

Study Design

The methodology of the German Diabetes and Dialysis Study (4D) was described previously.[17] Between March 1998 and October 2002, a total of 1,255 patients with ESRD were recruited from 178 dialysis units throughout Germany. All patients had type 2 diabetes mellitus, were aged 18 to 80 years, and were receiving maintenance hemodialysis with a dialysis vintage of less than 2 years at the time of randomization.

After a run-in period of 4 weeks, patients were randomly assigned to double-blind treatment with 20 mg of atorvastatin (n = 619) or placebo (n = 636). For the present post hoc analysis, we took a subpopulation of n = 1,034 patients with valid measurements of cardiac TnT measured using a high-sensitivity assay (hs-TnT) and a conventional assay (conventional TnT). At each follow-up visit until March 2004, information for any suspected end point or serious adverse event was assessed. Study visits occurred before randomization, at randomization, 4 weeks after the start of treatment, and then every 6 months.

The study was carried out according to the principles outlined in the Declaration of Helsinki. The respective medical ethics committees approved the study. Approval and consent cover the additional analysis. Participation was voluntary and all patients provided written informed consent.

Outcome End Points

The primary end point of 4D was a composite of the first occurrence of death from cardiac causes, myocardial infarction, or stroke. Mortality from any cause, sudden death, stroke, myocardial infarction (fatal or nonfatal), and other causes was defined as a secondary end point. All end points were centrally adjudicated by 3 members of the end point committee blinded to study treatment and according to predefined criteria.

For the present analysis, we chose 2 separate end points: (1) all-cause mortality and (2) cardiovascular events, that is, the composite 4D primary end point (cardiac death, myocardial infarction, and stroke). Categorization of these events was based on the primary classification of the 4D end point committee.

Blood Sampling and Analysis

Blood samples were taken at baseline and at each follow-up visit (every 6 months) before the initiation of dialysis and the administration of drugs. Routine and safety parameters were determined at all visits at the Department of Clinical Chemistry, University of Freiburg, Germany. Samples were stored at −80°C before further analysis.

Cardiac TnT was measured at baseline using a conventional assay and high-sensitivity assay in all patients with sufficient sample volume. The conventional assay (4th Generation TnT; Roche Diagnostics) had a limit of detection of 10 ng/L, a 99th percentile cutoff concentration of 10 ng/L, and lowest concentration with a coefficient of variation of 10% of 35 ng/L, the diagnostic cutoff suggested at that time for clinical practice.[18] The high-sensitivity assay (5th generation hs-TnT; Roche Diagnostics; performed on an Elecsys 2010 system) has a limit of detection of 5 ng/L, a 99th percentile cutoff concentration of 14 ng/L, and a coefficient of variation of 10% at 13 ng/L.

Comparing the 2 TnT assays, a concentration of 50 ng/L using the high-sensitivity assay represents the approximate cutoff concentration for the conventional assay.[19] In the conventional assay, the previously described tendency for higher values at the lower end of the measuring range is also seen in our data (Fig S1). Therefore, to evaluate the additional prognostic information of the high-sensitivity assay compared to the conventional assay, a subgroup analysis of patients with hs-TnT values < 50 ng/L was planned. These patients would have been classified as having normal TnT concentrations using the translated conventional assay cutoff.

Statistical Analysis

As appropriate, continuous variables were expressed as mean with standard deviation or median with interquartile range. Categorical variables were expressed as percentages. The association between hs-TnT and conventional TnT concentrations was analyzed including scatter plots and Pearson correlation coefficients. The study population was divided into 4 groups according to quartiles of hs-TnT concentrations. Absolute (incidence) rates were calculated and relative risks were derived from Cox regression analyses, that is, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Cox regression analyses were adjusted for potential confounders representing cardiovascular factors, including age, sex, atorvastatin medication, coronary artery disease, heart failure, smoking status, systolic blood pressure, low-density lipoprotein cholesterol concentration, body mass index, and history of transient ischemic attack, and for dialysis-related factors, including hemoglobin concentration, glycated hemoglobin concentration, phosphate concentration, ultrafiltration volume, albumin concentration, dialysis vintage, and presence of an arteriovenous fistula. For all mentioned covariates, we checked the proportionality assumption graphically by log-log plots and a proportional hazards test. For both end points, we fitted a sequence of Cox proportional hazards models (also called cause-specific hazards model considering the competing events as censored) including different adjusting variables (model 1: adjusted for age and sex only, model 2: additionally adjusted for cardiovascular factors, and model 3: additionally adjusted for dialysis-related factors). Within the defined subcohort, due to the lower number of events compared to the overall cohort, models 2 and 3 have to be interpreted cautiously.

In addition, for the end point cardiovascular events, we fitted as sensitivity analysis the Fine and Gray[20] competing-risk model (also called the subdistribution hazards models)

Download English Version:

https://daneshyari.com/en/article/8769752

Download Persian Version:

https://daneshyari.com/article/8769752

Daneshyari.com