SCIENTIFIC LETTER

Diagnostic specificity and prognostic value of cardiac troponins in asymptomatic chronic haemodialysis patients: a three year prospective study

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Diagnosis and risk stratification of coronary artery disease (CAD) are key issues in the management of haemodialysis patients. In patients with end stage renal disease (ESRD), the specificity of cardiac troponin T (cTnT) is low (< 80%) in contrast to cardiac troponin I (cTnI) (81–100%). However, in asymptomatic patients with ESRD, an increased cTnT concentration is associated with an increased risk of acute coronary syndrome (ACS), and while some studies have documented the same relation between cTnI and future ACS others have been inconclusive or negative.^{1–4} Discrepancies between these studies may be secondary to the type of assay used to measure cTnI, the cut off concentration used to categorise patients, the outcome measured, or the length of patient follow up. Since cTnI are likely to be favoured over cTnT in the acute care of patients with ESRD because of a higher specificity, the predictive value of this marker in asymptomatic patients is important to clarify. Our work aimed at comparing the prognostic value of cardiac troponins over a three year follow up in asymptomatic patients with ESRD.

METHODS

A three year prospective study was undertaken in February 2001 of all eligible patients on chronic haemodialysis in our hospital. Patients having presented with angina within the previous 14 days or with a diagnosis of ACS in the previous four weeks were excluded. Other exclusion criteria were pericarditis, pulmonary embolism in the previous 14 days, and a documented left ventricular ejection fraction < 25%. Demographic data were recorded for each patient as well as the number of months on dialysis, history of CAD, smoking, diabetes, hypertension, and hyperlipidaemia. The outcome was the occurrence of an ACS during follow up. cTnI was determined with a microparticle enzyme immunoassay (MEIA, AxSYM; Abbott Laboratories, Saint-Laurent, Quebec, Canada). The assay has a detection threshold of 0.3 µg/l with a recommended clinical threshold of 1.0 µg/l.⁵ cTnT was determined with the third generation Roche immunoassay (Elecsys 2010; Roche Diagnostics, Laval, Quebec, Canada), with a clinical threshold concentration for myocardial injury of 0.10 µg/l.⁵ The cardiac troponin concentrations measured to predict an ACS during follow up were depicted as receiver operating characteristic (ROC) curves and optimal cut off concentrations for troponins were determined from these plots. Kaplan-Meier curves with log rank analysis and Cox proportional hazard regression were used to determine variables associated with an ACS. Patients were censored at the time of kidney transplantation or non-cardiovascular death. Analyses were carried out with SPSS (SPSS Inc, Chicago, Illinois, USA) and MedCalc software packages (MedCalc, Mariakerke, Belgium).

Figure 1 Survival without an episode of acute coronary syndrome (ACS) in patients with or without a detectable concentration of cardiac troponin I (cTnI) (n = 101).

RESULTS

Twenty three of all chronic haemodialysis patients met our exclusion criteria. The remaining 101 patients were enrolled in the study. The median age was 66 years, 57% of the patients were men, 29% were diabetic, 85% were hypertensive, 29% were smokers, 27% were hyperlipidaemic, and 37% had a history of CAD. The median number of months on dialysis was 27 (range 1–236). The observed specificity was 99% for cTnI and 84% for cTnT.

During the three year follow up period, 29 patients had an ACS. The cTnI concentration optimised for diagnostic specificity and sensitivity for the prediction of an ACS during follow up (≥ 0.2 µg/l) was under the reproducible threshold and, therefore, we used the detection threshold of ≥ 0.3 µg/l as a cut off concentration for cTnI. Patients with a cTnI concentration ≥ 0.3 µg/l had an unadjusted hazard ratio of an ACS of 3.37 (95% confidence interval (CI) 1.56 to 7.25, $p = 0.001$) compared with those with an undetectable concentration (fig 1). However, the risk of a first ACS within the group with a detectable cTnI decreased over the three year follow up period and, hence, the proportional hazard assumption was not respected. The hazard ratio measured over the first half of follow up was 5.44 (95% CI 2.20 to 13.44).

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ESRD, end stage renal disease; ROC, receiver operating characteristic

$p < 0.001$) versus 0.80 (95% CI 0.10 to 6.29, not significant) in the second half. By comparison, the optimised cTnT concentration was $\geq 0.04 \mu\text{g/l}$ with an unadjusted hazard ratio of ACS of 2.98 (95% CI 1.04 to 8.57, $p = 0.04$). The risk of first ACS in the higher cTnT group also decreased over time. The hazard ratio measured over the first half of follow up was 4.78 (95% CI 1.72 to 13.29, $p = 0.003$) versus 2.35 (95% CI 0.68 to 8.12, not significant) in the second half. Both troponins were similarly predictive of an increased risk of ACS at 1.5 and three years' follow up with mean (SD) areas under the ROC curve at 1.5 years for cTnI and cTnT of 0.77 (0.06) and 0.73 (0.07), respectively ($p > 0.1$).

Higher age and a history of CAD were the only other variables statistically associated with a higher risk of ACS. Multivariate Cox regressions were limited to the first half of follow up and included only two variables at a time, given the number of events during that period. The hazard ratios for cTnI and cTnT expressed categorically according to optimised cut offs remained significant even after adjustment for any clinical variable measured (data not shown).

DISCUSSION

This study shows that cTnI was the most diagnostically specific cardiac troponin in our chronic haemodialysis population. Prognostically, the equally predictive value of cTnI and cTnT found in this work is concordant with other but not all studies. One study did not find an association between cTnI and cardiac admissions but this outcome included congestive heart failure.⁴ Congestive heart failure can be difficult to differentiate from volume overload in the ESRD population and may account for the high rate of cardiac admissions seen in that cohort. Another large study identified an optimised cTnI concentration of $0.03 \mu\text{g/l}$ by ROC curve analysis for the prediction of future myocardial infarction in asymptomatic patients with ESRD.³ However, since this concentration was below the detection threshold of the assay ($0.04 \mu\text{g/l}$), the authors elected to use a higher cut off based on a reference non-ESRD population and found no association between cTnI and cardiac events.

Interestingly, the risk of ACS associated with cTnI and cTnT decreased over time. This suggests that higher, albeit normal, troponin concentrations are markers of active but

asymptomatic CAD likely to progress to an ACS in the relatively near future.

In conclusion, cTnI is highly specific in patients with ESRD and detectable concentrations are associated with an increased risk of ACS. cTnT is less specific from a diagnostic standpoint but similarly predictive of the future risk of ACS.

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Ethics approval: The hospital Ethics Committee approved the protocol and all patients gave informed and written consent before entering the study.

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