Prognostic Value of Troponin T and I Among Asymptomatic Patients With End-Stage Renal Disease
A Meta-Analysis

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Background—The prognostic usefulness of troponin enzymes in end-stage renal disease (ESRD) patients is controversial. To resolve this uncertainty of troponin as a prognostic tool, we conducted a systematic review to quantify the association between elevated troponin I or T and long-term total mortality among ESRD patients not suspected of having acute coronary syndrome.

Methods and Results—We conducted an unrestricted search from the MEDLINE, EMBASE, and DARE bibliographic databases to December 2004 using the terms troponin.mp. or exp troponin and exp kidney, exp renal, exp kidney disease exp renal replacement therapy. We also manually searched review articles and bibliographies to supplement the search. Studies were included if they were prospective observational studies, used cardiac-specific troponin assays, and evaluated long-term risk of death or cardiac events for asymptomatic ESRD patients. Two authors independently abstracted data on study and patient characteristics. Studies findings were stratified according to troponin T or I levels. We used a random-effects model to pool study results and tested for heterogeneity using $\chi^2$ testing and used funnel-plot inspection to evaluate the presence of publication bias. Data from 28 studies (3931 patients) published between 1999 and December 2004 were included in this review. Patients received dialysis for a median duration of 4 years, with a mean follow-up of 23 months. From the pooled analysis, elevated troponin T ($>0.1$ ng/mL) was significantly associated with increased all-cause mortality (relative risk, 2.64; 95% CI, 2.17 to 3.20). Although the prognostic effect sizes were all consistent with a positive relationship between troponin T and mortality, there was significant heterogeneity in the magnitude of these effect sizes ($P=0.015$). The funnel plot showed evidence of publication bias. Elevated troponin T was also strongly associated with increased cardiac death. Studies evaluating troponin I included a wide variety of assays and differing cut points, rendering synthesis of the study findings difficult.

Conclusions—Elevated troponin T ($>0.1$ ng/mL) identifies a subgroup of ESRD patients who have poor survival and a high risk of cardiac death despite being asymptomatic. These findings suggest that troponin T is a promising risk stratification tool and may help frame therapeutic decisions. The clinical interpretation of elevated troponin I levels, however, remain unclear, largely because of the lack of standardization of assays. (Circulation. 2005;112:3088-3096.)

Key Words: kidney ■ mortality ■ troponin ■ meta-analysis

Cardiovascular disease accounts for approximately 50% of deaths in patients with end-stage renal disease (ESRD).1,2 Identifying those ESRD patients at high risk for future events is challenging, because they often have silent ischemia or atypical expressions of angina.3–5 Use of ECG data as diagnostic and prognostic tools is also difficult in this population because of the high prevalence of left ventricular hypertrophy and electrolyte disturbances, which themselves cause ECG abnormalities. Because traditional cardiac risk factors only partially account for the increased cardiovascular disease burden of ESRD patients, better tools for risk stratification are needed.

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Over the past decade, data have emerged that suggest that elevated cardiac-specific troponins may predict death among ESRD patients without symptoms of acute coronary syndrome. Although the mechanism of death is unknown, the cardiac-specific troponins T and I are expressed almost exclusively in cardiac muscle among patients with ESRD.6–9 Because troponin levels are widely used, the assays are relatively inexpensive and unaffected by dialysis10; these levels are a promising risk stratification tool. However, the
overall prognostic usefulness of the troponins remains unclear. Previous studies, based on retrospective study designs and multiple insensitive assays that cross-react with skeletal troponin, have produced conflicting results.

To help resolve this uncertainty of troponin as a prognostic tool, we conducted a systematic review to quantify the association between elevated troponin I or T and long-term total mortality among ESRD patients not suspected of having acute coronary syndrome. To avoid the limitations of previous published reviews,11,12 we included only prospective study designs, excluded studies using assays that cross-react with skeletal troponin, stratified the analysis by type of troponin assay (I versus T), and evaluated the impact of other prognostic variables besides troponin. To explore the mechanisms that potentially explain this relationship, we examined the additional outcome of cardiovascular death and described the relationship between troponin level and cardiovascular death in various prognostic subgroups. A defined level of cardiac-specific troponin elevation that accurately predicted adverse cardiovascular events would be an invaluable asset in therapeutic decision-making for patients with ESRD.

Methods

The methods used in this review are in accordance with the Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting.13

Research Objectives

The primary research objective was to determine, by use of systematic review techniques, whether elevated serum troponin I or T predicted higher long-term risk of cardiac death or all-cause mortality among asymptomatic patients with ESRD. A secondary objective was to assess whether study outcomes varied systematically with prognostic variables at the study level (history of cardiovascular disease, diabetes mellitus, or diabetic nephropathy; duration of dialysis; and length of follow-up).

Studies Included

To minimize differences between studies, we imposed the following methodological restrictions for the inclusion criteria: (1) prospective observational study design; and studies that (2) evaluated prognosis of patients with abnormal levels of either troponin I or T, (3) examined all-cause mortality or cardiac death, or (4) included only asymptomatic patients (ie, no symptoms of acute coronary syndrome).

We excluded studies based on qualitative assays or those that used first-generation assays of troponin T, which cross-react with skeletal muscle. Primary authors were contacted if the study did not report data amenable to the creation of 2×2 tables. (A rejection log is available on request.)

Finding Relevant Studies

To identify relevant studies, MEDLINE (OVID 1966–December 2004), EMBASE (1980–December 2004), the Cochrane review of systematic reviews, and the Database of Abstracts of Reviews of Effects (fourth quarter 2004) were reviewed without language restrictions. The search strategy, developed with an experienced librarian, included the following MeSH terms: troponin.mp or exp troponin and exp kidney, exp renal, exp kidney disease exp renal replacement therapy. We also manually reviewed the bibliographies of all relevant articles to supplement our search.

Quality Review and Data Abstraction

Two of the reviewers (N.A.K. and B.R.H.) independently reviewed each study for the quality review and abstracted data on study and patient characteristics as well as outcomes. Because there is no standardized quality scoring system for observational studies, the components of the quality review were derived largely from the Egger’s quality checklist for prognostic studies.14 Percentage agreement between the 2 reviewers on the 14 items on the quality review ranged from 77% to 100%. Disagreements were resolved by consensus.

Statistical Analysis

For studies evaluating more than 1 troponin I assay,15–17 only the most common manufacturer’s assay was reported. For studies evaluating more than 1 cut point,18–21 the most common cut point among the individual studies was used for analysis to improve between-study comparisons. To study the quality of the assays, we used the standards set by the European Society of Cardiology and the American College of Cardiology for the definition of myocardial injury.22 Troponin levels should exceed the 99th percentile value of the reference population to infer myocardial cell injury, the total imprecision at this decision level should not exceed 10%, and this level should be at least 5-fold higher than the lower limit of detection.

For assessment of data quality and data abstraction, percentage agreement between the 2 reviewers was calculated. Patient, study, and assay quality components and study description were summarized by use of basic descriptive statistics (simple counts and means). Meta-analyses of all outcomes are reported using random-effects models because fixed and random-effects model results were similar and random-effects models tend to produce more conservative estimates. A χ² test for heterogeneity was used to assess between-study heterogeneity. Pooled relative risks were expressed with 95% CIs. We also evaluated studies for publication bias by visually inspecting funnel plots and by the Egger test. From univariate regression analysis, we assessed whether the association between elevated troponins and all-cause mortality varied systematically with certain prognostic variables at the study level (history of cardiovascular disease, diabetes mellitus, or diabetic nephropathy; mean durations of dialysis; and length of follow-up). The regression model relates the prognostic effect of troponin T to the study level covariates, assuming a normal distribution for the residual errors with both a within-study and an additive between-studies component of variance, using an estimate that is based on the restricted maximum likelihood.

Values for some factors and the outcome of cardiac death were not available for several studies. For the outcomes of cardiac death and for each meta-regression, only studies whereby the information was available were included in the analysis. The analysis was performed by use of STATA statistical software (Version 7, intercooled, STATA Corp).

Results

Study Selection

From the search strategy, 80 full-text articles were retrieved. Of these, 28 studies met the inclusion criteria and were used for this review. The other 52 studies were excluded largely because they did not evaluate the prognosis of patients with abnormal levels of troponin (35/52), were retrospective analyses (5/52), did not report death or myocardial infarction as an outcome (3/52), evaluated patients with acute coronary syndrome (7/52), included an acute renal failure cohort (1/52), or evaluated the first-generation troponin T assay (1/52).

Methodological Quality

The 28 prospective observational studies were determined to be of fair quality. Of the primary studies, 100% had described independent, consecutive sampling of their cohort, and 64% had explicitly ascertained that patients did not have any acute
symptoms or signs of acute coronary syndrome. The majority of studies (75%) reported at least 1 cardiac risk factor, and 89% reported baseline cardiovascular history. However, only 18% of studies indicated the participants' baseline medication use. All studies described the troponin assays used, and most (82%) used prespecified, rather than data-dependent, cutoff values used to define normal and abnormal levels. Troponin values were known for all patients. Few studies however, explicitly indicated whether the outcomes or troponin measurements were blinded (35%), and only 1 study described any treatments or management of patients during follow-up. The majority (96%) of primary studies specified the number of patients lost to follow-up, with most (82%) reporting that no patients were lost to follow-up, and only 2 studies had losses that exceeded 20%.23,24

Description of Primary Studies
The 28 studies were published between 1999 and 2004 and included 3931 patients from 12 countries (Table 1). From all primary studies, 94% of patients were receiving hemodialysis. Of the total population, 58% were males and the median (or mean) ages of the cohorts ranged from 52 to 67 years. The median duration on dialysis was 4 years (interquartile range, 2.8 to 7.6 years). Patients were followed for an average of 23 months (range, 6 to 48 months). Table 1 demonstrates variability in prevalence of diabetes mellitus (or diabetic nephropathy), prior history of cardiovascular disease, length of follow-up of individual studies and mean number of years spent on dialysis across the individual studies.

Troponin T and I Assays
As discerned from Table 2, the troponin T assays were similar, and studies chose similar cut points (ie, >0.1 ng/mL) to detect abnormal levels. For the troponin T assays, this cut point is close to or greater than the threshold at which there is a 10% total coefficient of variance (ie, the lowest concentration at which 10% imprecision is achieved). This cut point is also >5-fold higher than the lower limit of detection. For the troponin I studies, investigators used multiple different manufacturer assays and varying cut points. Approximately

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<th>Mean No. of Years on HD/PD†</th>
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*Medan value.
†HD indicates hemodialysis, PD, peritoneal dialysis.
half of these chosen cut points were less than 5-fold higher than the lower limit of detection, and only 63% were above the threshold associated with a 10% total coefficient of variation.

**Association of Troponin T With Major Outcomes**

There were 17 primary studies evaluating the association between troponin T and all-cause mortality. In the forest plot of individual prognostic effect sizes in Figure 1, the lower boundaries of the 95% CIs of almost all trials were greater than 1, suggesting a consistent association between troponin and all-cause mortality. The two 95% CIs that crossed 1 were also wide because of the small sample size and low event rates from these studies. From the pooled analysis, elevated troponin T was significantly associated with increased all-cause mortality (relative risk RR, 2.64; 95% CI, 2.17 to 3.20). Although the prognostic effect sizes were all consistent with a positive relationship between troponin T and mortality, there was significant heterogeneity (P<0.015) in the magnitude of these effect sizes. The funnel plot (Figure 2) showed evidence of publication bias.
bias. When we removed the largest study, by Apple and colleagues, heterogeneity among the remaining studies was no longer significant. The study by Apple and colleagues demonstrated a strong association between troponin T and total mortality (RR, 1.72; 95% CI, 1.38 to 2.13). Apple’s study was similar in quality and methodology to the remaining studies except that the patient sample had a shorter mean duration of dialysis (1.6 years).

There were 8 studies that evaluated the outcome of cardiac death. As depicted in Figure 3, each of these primary studies
demonstrated an association between elevated troponin T and cardiac death. Elevated troponin T was strongly associated with a significant increase in long-term cardiac death (RR, 2.55; 95% CI, 1.93 to 3.37; \( P < 0.001 \)).

In the sensitivity analysis, effect sizes for troponin T and total mortality were similar when studies that had optimized cut points rather than a priori cut points were removed.\(^{21,26–29}\) Effect sizes were also similar when studies that evaluated nonhemodialysis patients\(^{30}\) and had >20% loss to follow-up\(^{22,23}\) were removed.

**Association of Troponin I With Major Outcomes**

From the 12 studies examining troponin I, elevated troponin I was associated with increased total mortality (RR, 1.74; 95% CI, 1.27 to 2.38; \( P = 0.001 \)) (Figure 4). The \( \chi^2 \) test for heterogeneity was nonsignificant. However, given the varying assays and cut points used for troponin I assays, mathematically pooled results should be interpreted with caution. We report this pooled result because this is the current best available evidence for clinical practice in those institutions using troponin I assays exclusively, and these results may guide other investigators studying troponin I in ESRD patients. Furthermore, as discerned in Figure 5, the estimates of cardiac death risk were highly variable among the 6 studies evaluating troponin I.

**Other Prognostic Characteristics**

Seventy-two percent of the primary studies adjusted for other prognostic factors to determine independent associations of troponin with all-cause mortality. Of the 16 troponin T studies that controlled for multiple prognostic factors, 15 demonstrated an independent association between elevated troponin T and all-cause mortality. The majority of these studies controlled for advanced age and presence of cardiovascular disease and diabetes mellitus, all factors strongly associated with mortality. Elevated troponin T was also independently associated with mortality when adjusted for the presence of left ventricular hypertrophy\(^{21,26,31}\) and left ventricular dysfunction.\(^{26,32,33}\) Troponin I remained independently associated with mortality in only 2 of 8 troponin I studies that controlled for confounding variables.

For troponin T, longer duration of dialysis and longer length of follow-up were associated with an increase in prognostic effect size in both univariate and multivariate meta-regression analyses. The proportion of patients with a history of cardiovascular disease or the presence of diabetes mellitus or diabetic nephropathy did not influence the association between troponin T and all-cause mortality. However,
when Apple's study was removed, none of the prognostic factors were associated with a significant change in prognostic effect size.

**Discussion**

The primary studies found moderate to large increases in risk of cardiac death and all-cause mortality with elevated troponin T among asymptomatic ESRD patients. Our analysis found heterogeneity in the estimates of prognosis and evidence for publication bias, suggesting that the actual pooled estimate for mortality is more modest. However, even considering the outlier study by Apple et al, the association with troponin T and mortality remains significant. The sensitivity analysis and the independent association of troponin T despite adjustment for other prognostic factors support the overall association between elevated troponin T and long-term mortality. A modest association between troponin T and mortality in an asymptomatic population that is otherwise challenging to risk-stratify may have clinical usefulness.

The fraction of troponin-positive patients with ESRD is influenced by the assay technology and the discriminator value chosen. Troponin T assays are produced by a single manufacturer, thereby standardizing the assay results. The decision cut point for these troponin T studies was generally 0.1 ng/mL, above both the reference population threshold (0.01 ng/mL) for cardiac injury and the threshold associated with a 10% coefficient of variation, indicating reasonable precision at the 0.1 ng/mL level. This cut point is also consistent with other major prognostic studies of patients with acute coronary syndrome with and without chronic kidney disease.

For the troponin I studies, investigators used multiple different manufacturer assays and varying cut points. Although the troponin I studies were similar in design, patient population, and outcome, this lack of standardization as well as wide differences in the development of each troponin I assay gave rise to major concerns about our ability to mathematically synthesize these results. Although individual studies generally showed an association between troponin I and long-term all-cause mortality, adjustment for other prognostic factors in these studies did not demonstrate an independent association between troponin I and long-term mortality. These findings suggest that troponin I may not be a viable marker for predicting outcomes. Thus, the controversy surrounding the association between troponin I and all-cause mortality is justified, and the best available evidence does not clarify this association.

Understanding the mechanisms that underlie elevation in troponin T levels among ESRD patients is of particular importance to help frame appropriate therapeutic decisions. In non-ESRD patients, troponin isoenzymes are an extremely sensitive and specific marker for myocardial cell injury. Previous authors have suggested that the mechanism for a rise in troponin among ESRD patients was a result of noncardiac causes, such as uremic myopathy. However, multiple studies were unable to identify troponin in noncardiac organs, and our analysis demonstrates a strong association between elevation in troponin T and cardiac death. Troponin T may detect subclinical myocardial cell injury during the repetitive cardiac stresses provoked by hemodialysis. In addition, other relative ischemic stresses might include undetected heart failure or myocardial remodeling in the setting of left ventricular hypertrophy. Several studies reported an association with elevated troponin T and left ventricular mass index.

However, as several studies also determined, elevated troponin T remained associated with total mortality despite adjustment for the presence of left ventricular hypertrophy or left ventricular dysfunction. In a prespecified subgroup analysis, deFilippi and colleagues reported that multivessel coronary artery disease diagnosed by angiography was more prevalent with progressively greater quartiles of troponin T. Our analysis demonstrates a strong relationship between elevated troponin T and cardiac death; however, additional mechanisms underlying the increased long-term mortality need to be explored.

This systematic review serves to clarify the association between troponin T and long-term all-cause mortality in asymptomatic ESRD patients using a large pool of studies and also identified a strong association between troponin T and cardiac death, implying a cardiovascular mechanism of death. The association between elevated troponin T and all-cause mortality is concordant with an earlier review that combined 4 troponin T studies.

There are several limitations to this study. The primary studies had several methodological flaws, including lack of reporting of blinding and treatment subsequent to entry into the studies, which may have introduced bias into the results. Although we conducted an unrestricted literature search that included the Database of Abstracts of Reviews of Effects, there was most likely publication bias in the troponin T analyses whereby larger trials had lower estimates of prognosis compared with smaller studies. This bias would tend to
overinflate the pooled estimate of prognosis. However, almost all studies, including the largest study, by Apple et al, did demonstrate a significant association between troponin T and mortality. Most troponin levels were ascertained from a single measurement, rather than an average of repeated measurements over time. Thus, given the recognized measurement error of biological variables, the true magnitude of association between troponin and mortality may be greater. Although the primary studies did not each statistically adjust for identical covariates or all prognostic factors, most studies controlled for similar and clinically important prognostic variables (eg, age, cardiovascular disease, and diabetes mellitus). Also, an important caveat of this study was that the mortality risks were long term, and association with short-term mortality or diagnosis of acute myocardial infarction using troponin T is unclear.

Conclusions
It is often difficult to risk-stratify stable, asymptomatic ESRD patients without the use of costly noninvasive or invasive cardiac studies. Troponin T is a promising prognostic tool, because elevated levels identify a subset of ESRD patients who have poor survival and higher risk of cardiac death. Furthermore, the assays are standardized and readily available. The prognostic usefulness of troponin I, however, remain unclear, largely because of the lack of standardization of assays. Thus, currently, troponin I should not be used to prognosticate risk in this patient population. This analysis corroborates previous postulates that a cardiovascular cause underlies the association between mortality and elevated troponin T. Future studies are needed to elucidate the specific pathogenic mechanisms, and the impact of potential therapeutic interventions.

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References
Clinical Perspective

Whether cardiac-specific troponin enzymes can predict death among patients with end-stage renal disease (ESRD) is unclear. To resolve this uncertainty, we conducted a systematic review to quantify the association between elevated troponin I or T and long-term total mortality among ESRD patients not suspected of having acute coronary syndrome. From 17 studies, we found that elevated troponin T (>0.1 ng/mL) is significantly associated with increased all-cause mortality (relative risk, 2.64; 95% CI, 2.17 to 3.20). Although the prognostic effect sizes were all consistent with a positive relationship between troponin T and mortality, there was significant heterogeneity in the magnitude of these effect sizes (P = 0.015). Elevated troponin T was also strongly associated with increased cardiac death. Studies evaluating troponin I included a wide variety of assays and differing cut points, rendering synthesis of the study findings difficult. Identifying those ESRD patients at high risk for future events is challenging, because they often have silent ischemia or atypical expressions of angina. Elevated troponin T (>0.1 ng/mL) identifies a subgroup of ESRD patients who have poor survival and a high risk of cardiac death despite being asymptomatic. These findings suggest that troponin T is a promising risk stratification tool and may help frame therapeutic decisions. The clinical interpretation of elevated troponin I levels, however, remains unclear, largely because of the lack of standardization of assays.
Prognostic Value of Troponin T and I Among Asymptomatic Patients With End-Stage Renal Disease: A Meta-Analysis
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