Elevated Cardiac Troponin T Is Associated With Higher Mortality and Amputation Rates in Patients With Peripheral Arterial Disease

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Objectives
The aim of the present study was to evaluate whether elevated cardiac troponin T (cTnT) was independently associated with an increased all-cause mortality or risk of cardiovascular events and amputation among patients with peripheral arterial disease (PAD).

Background
PAD patients often have impaired renal function, and the blood concentration of cardiac troponin often increases with declining glomerular filtration rate.

Methods
The cohort consisted of 1,041 consecutive PAD patients (653 males, 388 females, age 70.7 ± 10.8 years, Rutherford stages 2 to 5) undergoing endovascular peripheral revascularization.

Results
At baseline, measurable cTnT levels (>0.01 ng/ml) were detected in 21.3% of individuals. Compared with patients who had undetectable cTnT levels, those with cTnT levels >0.01 ng/ml had higher rates for mortality (31.7% vs. 3.9%, respectively; p < 0.001), myocardial infarction (4.1% vs. 1.1%, respectively; p = 0.003), and amputation (10.1% vs. 2.4%, respectively; p < 0.001) during a 1-year follow-up. In adjusted Cox regression models, cTnT levels >0.01 ng/ml were associated with increased total mortality (hazard ratio [HR]: 8.14; 95% confidence interval [CI]: 3.77 to 17.6; p < 0.001) and amputation rates (HR: 3.71; 95% CI: 1.33 to 10.3; p = 0.012).

Conclusions
cTnT is frequently elevated in PAD patients and is associated with higher event rates in terms of total mortality and amputation. Even small cTnT elevations predict a markedly increased risk that is independent of an impaired renal function. (Troponin T as Risk Stratification Tool in Patients With Peripheral Arterial Occlusive Disease; NCT01087385) J Am Coll Cardiol 2014;63:1529–38 © 2014 by the American College of Cardiology Foundation

Cardiac troponin T (cTnT) is a component of the contractile apparatus of cardiomyocytes and an established sensitive biomarker of myocardial cell injury. Therefore, testing for this biomarker is recommended for the diagnosis of myocardial infarction in the clinical setting of an acute coronary syndrome (ACS) (1). An elevated cTnT level is associated with an adverse outcome after ACS (2,3) in patients with chronic heart failure (4,5), acute pulmonary embolism (6), and end-stage renal disease (ESRD) (7,8) and in the general population (9–12). The clinical significance of detectable cTnT among patients with peripheral arterial occlusive disease (PAD) is unknown. Recently, some investigations have reported that elevated cTnT levels may also be of prognostic value in patients with acute limb ischemia (13,14). However, cardiac troponin levels often increase with a declining glomerular filtration rate, and many PAD patients have impaired renal function (15,16).

There is evidence that chronic kidney disease itself is associated with an increased cardiovascular mortality (17,18). Elevated cTnT levels are also associated with other vascular risk factors, such as age, male sex, and diabetes (9,19,20). This study was performed to define the distribution and determinants of measurable cTnT among symptomatic PAD patients and to explore its prognostic impact on mortality, amputation rates, and cardiovascular outcomes during follow-up.

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Methods

Study design and participants. This retrospective single-center study enrolled 1,065 consecutive symptomatic PAD patients at Rutherford stages 2 to 5 (Fontaine stages IIb to IV). Patients were admitted to our university teaching hospital between January 2007 and December 2007 for urgent or elective endovascular revascularization. The ankle-brachial index and diagnostic workup by a color-coded duplex scan were routinely used before angiography to confirm the diagnosis of PAD and to determine the therapeutic strategy. All patients were followed for a period of at least 12 months or until death. Most of the patients were regularly seen in the outpatient department for diagnostic follow-up and were asked to answer a standardized questionnaire. To obtain information about mortality and vascular morbidity, we reviewed medical records and contacted the patients and their general practitioners. Outcome data were available for 1,012 patients (95.0%) (Fig. 1). The protocol was approved by the local ethics committee and registered at ClinicalTrials.Gov (NCT01087385).

The exclusion criteria were all conditions that may acutely increase cTnT levels. Myocardial ischemia or clinical symptoms indicating unstable angina pectoris or ACS within the previous 14 days resulted in exclusion from analysis. Additional exclusion criteria were acute pulmonary embolism, aortic dissection, New York Heart Association functional class III or IV heart failure, cardiomyopathy, endocarditis, external electrical cardioversion for atrial fibrillation, and heart surgery within the previous 14 days. By contrast, chronic kidney disease (CKD) and impaired renal function were not exclusion criteria.

Laboratory assessment. Blood samples were collected upon hospital admission. cTnT was measured with the fourth-generation assay Elecsys troponin T using a Cobas 6000 e601 system (Roche Diagnostics, Mannheim, Germany) according to the recommendations of the manufacturer. The 99th percentile value for the reference population used by the manufacturer of the assay was 0.01 ng/ml, and the lowest level at which the coefficient of variation was <10% was 0.03 ng/ml (21). A cutoff value of 0.01 ng/ml, which corresponds to the 99th percentile of a reference population and the lowest level of detection, was chosen to define an elevated cTnT level (22). Measurement of cTnT was routinely performed in all PAD patients upon hospital admission. However, the cTnT values were missing for 7 patients, who were censored from further statistical analysis (Fig. 1).

In addition, laboratory testing included automated and standardized testing of serum creatinine levels. The estimated glomerular filtration rate (eGFR) was determined by the Cockcroft-Gault formula and classified using standards set forth by the National Kidney Foundation Disease Outcomes Quality Initiative (23). According to these standards, we defined an impaired renal function as an eGFR concentration of <60 ml/min.

Baseline characteristics, comorbidities, and medication. Assessment of atherosclerotic disease and cardiovascular risk

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**Figure 1** Study Design

ACS = acute coronary syndrome(s); cTnT = cardiac troponin T; PAD = peripheral arterial disease.
factors was based on clinical history, clinical examination, and laboratory test results. Patients were interviewed about a history of coronary heart disease, ischemic cerebral infarction or transient ischemic attack, and PAD. Patients’ smoking status, classified as currently smoking versus never or previously smoked combined, was obtained using a standardized questionnaire. Diabetes mellitus was diagnosed in accordance with the World Health Organization classification (24). Arterial hypertension was defined by a systolic blood pressure of more than 140 mm Hg, a diastolic blood pressure of more than 90 mm Hg, or both on at least 2 occasions or by the use of antihypertensive drugs (25). Hypercholesterolemia was defined as a fasting cholesterol level exceeding 200 mg/dl, a low-density lipoprotein cholesterol level of at least 130 mg/dl, or both on at least 2 occasions or by the use of lipid-lowering drugs (26). Finally, patient medications were also recorded.

Clinical evaluation and ECG registration. Seventeen patients in the initial cohort had had an ACS within the previous 14 days before study entry and were censored from further statistical analysis (Fig. 1). There was no clinical evidence of myocardial ischemia among the remaining patients. We analyzed the patients’ electrocardiograms (ECG), which were performed simultaneously with blood sampling at the time of admission to the hospital. According to the consensus document of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), World Heart Federation (WHF) Task Force for the Redefinition of Myocardial Infarction (1), we registered ECG changes that might be indicative of acute myocardial ischemia, for example: 1) ST-segment elevation at the J-point in 2 contiguous leads with the cut-off points of ≥0.2 mV in men or ≥0.15 mV in women in leads V2 to V3 and/or ≥0.1 mV in other leads; 2) horizontal or down-sloping ST-segment depression of ≥0.05 mV and/or T-wave inversion of ≥0.1 mV in 2 contiguous leads; and 3) the presence of left bundle branch block.

Patient outcomes. Differences between outcomes after 12 months were determined for patients with elevated and those with normal cTnT concentrations. The primary outcomes examined in this analysis included total mortality and amputation. Secondary outcomes included myocardial infarction, ACS, and target limb revascularization. ACS was defined as a non–ST-segment and ST-segment myocardial infarction or unstable angina resulting in admission to the hospital. All reported events were confirmed by a review of medical records.

Statistical analysis. If not stated otherwise, the statistical analysis was performed using Statistical Package for Social Sciences (SPSS Statistics version 20.0, IBM, Chicago, Illinois). The baseline characteristics are reported as percentages for categorical variables and mean ± SD for continuous variables. We used the chi-square test in cross-tabulations and the Mann-Whitney U test to compare metric variables. Differences in outcomes were compared between patients with elevated and those with normal cTnT concentrations. Cox proportional hazards models were used to examine the relationship between the cTnT levels determined at baseline and the outcome events. In these models, the cTnT level was examined as a categorical variable. The Cox models sequentially added age, eGFR, and the presence or absence of current smoking, diabetes, and critical limb ischemia (CLI). Age and eGFR were modeled as continuous variables. The final model also included all patients with ECG changes conformable with acute myocardial ischemia, according to the latest consensus document of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction (1). All tests were 2-sided, and the criterion for statistical significance was a p value of <0.05.

Under conditions of competing risks, Cox regression models can produce misleading results, so a competing risk approach implemented in the software survival of R version 2.14.0 (R Development Team, R Foundation for Statistical Computing, Vienna, Austria) was used. We plotted the overall cumulative incidence of amputation outcomes and mortality (death before and after amputation) stratified by cTnT levels of <0.01 ng/ml and ≥0.01 ng/ml. Differences in curves were tested using the log-rank test. Furthermore, a reclassification analysis was performed using the Hmisc software package of R by Frank E. Harrell to quantify and compare the concordance of different predictors for mortality.

Results

Baseline characteristics of the study cohort. The clinical characteristics and demographic information available for the definitive study cohort of 1,041 patients are summarized in Table 1. The mean age of patients was 70.7 (±10.8) years; and 62.7% were males, 44.9% were known to have coronary artery disease (CAD), and 12.0% had a history of cerebral infarction.

Determinants of elevated troponin T. cTnT was detectable (≥0.01 ng/ml) in 222 patients (21.3%). Patients with cTnT values ≥0.01 ng/ml were older, more likely to be male or diabetic, and less likely to have hypercholesterolemia or to be current smokers compared with patients with cTnT values <0.01 ng/ml. An elevated cTnT concentration was also associated with an impaired renal function (Fig. 2), cardio- and cerebrovascular comorbidities, and severe PAD. In patients with intermittent claudication (i.e., Rutherford stages 2 and 3), a cTnT of ≥0.01 ng/ml was present in 54 of 623 cases (8.7%) compared with 168 of 418 patients (40.2%) with CLI (i.e., Rutherford stages 4 and 5; p < 0.001). In addition, PAD was localized more distally among patients with a cTnT elevation. In 121 cases (54.5%), the revascularization procedure involved the tibial or peroneal arteries compared with 272 cases (33.2%) of patients with undetectable cTnT (p < 0.001) (Table 1).

One-year outcomes. During a 1-year follow-up, 106 patients died (9.7%). In 14 patients (1.4%), a major amputation was unavoidable, and 29 patients (2.9%) underwent minor amputation. The overall amputation rate was 4.1% (Table 2).
Due to the progression of PAD, subsequent peripheral revascularization procedures were required, and target limb revascularization was performed in 24.3% of patients. Myocardial infarction occurred in 1.9% of patients during follow-up, and 4.6% of patients were hospitalized with an ACS.

Total mortality and amputation risk according to troponin T. Detectable cTnT levels ranged from 0.010 to 0.482 ng/ml. The distributions of cTnT by total mortality, cardiac events, and amputation are demonstrated in Figure 3.

The mortality and amputation rates in patients with elevated cTnT (≥0.01 ng/ml) were increased compared with those with normal cTnT (Table 2), resulting in an unadjusted hazard ratio (HR) of 9.87 (95% confidence interval [CI]: 6.49 to 15.0) for total mortality and 4.92 (95% CI: 2.68 to 9.03) for amputation.

The cumulative incidence curves for amputation outcomes and mortality (death before and after amputation) stratified by cTnT <0.01 ng/ml and ≥0.01 ng/ml are demonstrated in Figure 4. Comparing 1-year outcomes between patients with cTnT values ≥0.01 ng/ml and those with <0.01 ng/ml, mortality risk was 32.9% vs. 4.0% (log-rank test, p < 0.001), respectively, and the risk of amputation was 9.9% vs. 2.4% (log-rank test, p < 0.001), respectively.

No differences were observed for the incidence of peripheral revascularization procedures. Regarding mortality, similar associations were observed in a subgroup

| Table 1 Characteristics of the Study Sample by Baseline Troponin T Concentration |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Parameter                        | Total Cohort (N = 1,041) | cTnT <0.01 ng/ml (n = 819) | cTnT ≥0.01 ng/ml (n = 222) | p Value        |
| Demographics                     |                            |                              |                             |                |
| Age, yrs                         | 70.7 ± 10.8              | 69.7 ± 10.8                  | 74.5 ± 10.1                  | <0.001         |
| Males                            | 653 (62.7%)              | 498 (60.8%)                  | 155 (69.8%)                  | 0.015          |
| Vascular risk factors and comorbidities |                           |                              |                             |                |
| Current smoking                  | 251 (24.1%)              | 234 (28.6%)                  | 17 (7.7%)                   | <0.001         |
| Diabetes mellitus                | 424 (40.7%)              | 299 (36.5%)                  | 125 (56.3%)                  | <0.001         |
| Arterial hypertension            | 889 (85.4%)              | 690 (84.2%)                  | 199 (89.6%)                  | 0.044          |
| Hypercholesterolemia             | 828 (79.5%)              | 662 (80.8%)                  | 166 (74.8%)                  | 0.049          |
| Coronary artery disease          | 467 (44.9%)              | 333 (40.7%)                  | 134 (60.4%)                  | <0.001         |
| Prior cerebral infarction        | 125 (12.0%)              | 85 (10.4%)                   | 40 (18.0%)                   | 0.003          |
| Prior peripheral vascular intervention | 470 (45.1%)              | 378 (46.2%)                  | 92 (41.4%)                   | 0.224          |
| Prior peripheral bypass surgery  | 87 (8.4%)                | 73 (8.9%)                    | 14 (6.3%)                    | 0.273          |
| Prior amputation                 | 82 (7.9%)                | 48 (5.9%)                    | 34 (15.3%)                   | <0.001         |
| Chronic kidney disease (stages 3 to 5) | 400 (38.4%)              | 237 (28.9%)                  | 163 (73.4%)                  | <0.001         |
| End-stage renal failure          | 66 (6.3%)                | 5 (0.6%)                     | 61 (27.5%)                   | <0.001         |
| PAD characteristics              |                            |                              |                             |                |
| Rutherford category 2            | 287 (27.6%)              | 259 (31.6%)                  | 28 (12.6%)                   | <0.001         |
| Rutherford category 3            | 336 (32.3%)              | 310 (37.9%)                  | 26 (11.7%)                   | —              |
| Rutherford category 4            | 128 (12.3%)              | 94 (11.5%)                   | 34 (15.3%)                   | —              |
| Rutherford category 5            | 290 (27.9%)              | 156 (19.0%)                  | 134 (60.4%)                  | —              |
| Revascularized arterial segments |                            |                              |                             |                |
| Iliac artery                     | 224 (21.5%)              | 192 (23.4%)                  | 32 (14.4%)                   | 0.003          |
| Femoropopliteal artery           | 773 (74.3%)              | 612 (74.7%)                  | 161 (72.5%)                  | 0.545          |
| Tibial or peroneal artery        | 393 (37.8%)              | 272 (33.2%)                  | 121 (54.5%)                  | <0.001         |
| Endovascular revascularization procedures |                        |                              |                             |                |
| Occlusion/recanalization          | 547 (52.5%)              | 427 (52.1%)                  | 120 (54.1%)                  | 0.650          |
| PBOA                             | 170 (16.3%)              | 122 (14.9%)                  | 48 (78.4%)                   | 0.019          |
| Bare-metal stent                 | 882 (84.7%)              | 700 (85.5%)                  | 182 (92.0%)                  | 0.207          |
| Drug-eluting stent               | 182 (17.5%)              | 144 (17.6%)                  | 38 (17.1%)                   | 0.921          |
| Mechanical atherectomy           | 97 (9.3%)                | 83 (10.1%)                   | 14 (6.3%)                    | 0.091          |
| Mechanical thrombectomy          | 65 (6.2%)                | 50 (6.1%)                    | 15 (6.8%)                    | 0.754          |
| Local thrombolysis               | 64 (6.1%)                | 54 (6.6%)                    | 10 (4.5%)                    | 0.344          |
| Bypass surgery                   | 20 (1.9%)                | 16 (2.0%)                    | 4 (1.8%)                     | 0.978          |
| Medication at discharge          |                            |                              |                             |                |
| Aspirin or other antiplatelet medication | 997 (96.8%)              | 797 (97.4%)                  | 200 (94.3%)                  | 0.029          |
| Vitamin K antagonists            | 212 (20.4%)              | 141 (17.2%)                  | 71 (33.5%)                   | <0.001         |
| Beta-blocker                     | 611 (59.4%)              | 462 (56.5%)                  | 149 (70.6%)                  | <0.001         |
| ACE inhibitor or AT1 receptor antagonist | 732 (70.3%)              | 581 (70.9%)                  | 151 (68.0%)                  | 0.408          |
| Lipid-lowering drug              | 752 (72.2%)              | 631 (77.1%)                  | 121 (57.1%)                  | <0.001         |

Values are n (%). p Values refer to comparisons between patients with and those without elevated troponin T.

ACE = angiotensin-converting enzyme; AT1 = angiotensin type-1; cTnT = cardiac troponin T; PAD = peripheral arterial disease; PBOA = plain old balloon angioplasty.
analysis of patients with CLI (HR: 9.51; 95% CI: 3.94 to 23.0) and patients with intermittent claudication (HR: 5.01; 95% CI: 3.08 to 8.17). A corresponding subgroup analysis for amputation was not meaningful because only 2 amputations were performed in the subgroup of patients with intermittent claudication.

After adjusting for age, eGFR and the presence or absence of current smoking, diabetes, and CLI (Model 2), the mortality risk in the total cohort remained increased, with cTnT $\geq 0.01$ ng/ml (HR: 4.64; 95% CI: 2.82 to 7.64; $p < 0.001$). However, in multivariate analysis, the amputation risk was no longer significant (HR: 1.86; 95% CI: 0.92 to 3.74; $p = 0.083$) (Table 3).

The introduction of cTnT improved the prognostic discrimination for mortality outcomes. The addition of cTnT to Model 2 (c-statistic: 0.802 $\pm$ 0.039) offered moderate improvement (c-statistic with cTnT: 0.835 $\pm$ 0.036). Quantifying and comparing Harrell’s concordance, cTnT led to an improvement of risk reclassification (U-statistic: 0.30 $\pm$ 0.06).

No patient at baseline included in this analysis had clinical symptoms of unstable angina. Patients with an ACS within the previous 14 days before blood sampling had been excluded from the analysis. However, the interpretation of ECGs performed upon admission to hospital revealed significant differences in the frequencies of ECG criteria conformable with acute myocardial ischemia among patients with and without elevated cTnT (Table 4). Repeating the analysis after exclusion of all patients with any ECG changes suggestive of acute myocardial ischemia (Model 3), the HRs (and corresponding 95% CIs) were 8.14 (95% CI: 3.77 to 17.6; $p < 0.001$) for total mortality and 3.71 (95% CI: 1.33 to 10.3; $p = 0.012$) for amputation.

**Troponin T and myocardial infarction.** During the 1-year follow-up, we registered a total of 20 myocardial infarctions (1.9%). Unadjusted analysis revealed a risk of myocardial infarction for patients with cTnT values $\geq 0.01$ ng/ml (HR: 3.75; 95% CI: 1.55 to 9.05) (Table 2). After adjusting for age and eGFR, the association remained significant (HR: 3.40; 95% CI: 1.23 to 9.45; $p = 0.019$) (Model 1). In the final model after exclusion of all patients with ECG changes that might indicate acute myocardial ischemia (Model 3), these associations were no longer significant (HR: 3.44; 95% CI: 0.86 to 13.7; $p = 0.080$).

**Table 2 1-Year Mortality Rates and Incidence of Primary and Secondary Outcomes According to Cardiac Troponin T at Baseline**

<table>
<thead>
<tr>
<th>Event</th>
<th>No. in Total Cohort (%)</th>
<th>No. of cTnT $&lt; 0.01$ ng/ml (%)</th>
<th>No. of cTnT $\geq 0.01$ ng/ml (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>106 (9.7)</td>
<td>33 (3.9)</td>
<td>73 (31.7)</td>
<td>9.87 (6.49–15.0)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Amputation</td>
<td>42 (4.1)</td>
<td>20 (2.4)</td>
<td>22 (10.1)</td>
<td>4.92 (2.68–9.03)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Death or amputation</td>
<td>139 (12.9)</td>
<td>51 (6.1)</td>
<td>88 (38.5)</td>
<td>7.84 (5.62–11.1)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Target limb revascularization</td>
<td>252 (24.3)</td>
<td>204 (24.9)</td>
<td>48 (22.0)</td>
<td>1.10 (0.80–1.50)</td>
<td>0.563</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>20 (1.9)</td>
<td>11 (1.1)</td>
<td>9 (4.1)</td>
<td>3.75 (1.55–9.05)</td>
<td>0.003</td>
</tr>
<tr>
<td>ACS</td>
<td>48 (4.6)</td>
<td>36 (4.4)</td>
<td>12 (5.5)</td>
<td>1.56 (0.81–3.00)</td>
<td>0.182</td>
</tr>
</tbody>
</table>

Values are n (%).

ACS — acute coronary syndrome(s); CI — confidence interval; cTnT — cardiac troponin T; HR — hazard ratio.
Discussion

In this study, we examined the associations between elevated cTnT with total mortality and vascular outcomes in PAD patients who underwent an angiographic workup and a primary endovascular therapeutic approach for disease stages 2 to 5 of the Rutherford classification. Importantly, we assessed patients without clinical evidence of acute myocardial ischemia, according to the latest version of the ESC/ACCF/AHA/WHF redefinition of myocardial infarction consensus document (1). Detectable cTnT levels (>0.01 ng/ml) were observed in 21.3% of subjects in our cohort of symptomatic PAD patients. Elevated versus normal cTnT levels, as defined by the lower limit of detection using the conventional fourth-generation cTnT assay, was associated with several established vascular risk factors (i.e., age, male sex, diabetes, and CKD) and with an increased risk of death and amputation during follow-up. Adjusting for potential confounders such as age, eGFR and the presence or absence of current smoking, diabetes, and CLI did not impair this relationship. The cutoff level of >0.01 ng/ml revealed an 8.1-fold (95% CI: 3.8 to 17.6) increased mortality risk and a 3.7-fold (95% CI: 1.3 to 10.3) amputation risk among PAD patients.

Conversely, the associations between cTnT concentrations and myocardial infarction were not significant in our final model after adjusting for all potential confounding factors. A similar observation has been made by Omland et al. (27), who analyzed a cohort of 3,679 patients with stable CAD. In their study, cTnT levels measured with a high-sensitivity assay were detectable in 97.7% of CAD
patients. Although increasing cTnT values were independently related to higher mortality and heart failure rates during a 5-year follow-up, no independent association was observed between cTnT and myocardial infarction (27). This finding is in contrast to observations in patients with ACS in whom cTnT concentrations are considered biomarkers of myocardial injury due to plaque rupture, intra-coronary thrombosis, and myocardial ischemia and have been demonstrated to predict negative outcomes (2).

The plasma cTnT levels in healthy subjects are thought to result from a continuous microscopic loss of cardiomyocytes during normal life (28). There is evidence that detectable cTnT in subjects without clinical signs of acute myocardial ischemia indicates an increased risk for future cardiovascular events and unfavorable outcomes. The prevalence of cTnT values ≥0.01 ng/ml in 3,557 subjects of the population-based Dallas Heart Study was as low as 0.7% (9). That study investigated cTnT levels with a conventional fourth-generation cTnT assay, which was also used in our study. Detectable cTnT levels were typically associated with high-risk conditions, such as diabetes and advanced CKD. Moreover, elevated cTnT levels correlated with the presence of structural heart disease (e.g., left ventricular hypertrophy or dysfunction) and a subsequent risk of all-cause mortality (9,10,29).

Elevated concentrations of cardiac troponin are often observed in patients with advanced CKD, but without clinical signs of myocardial ischemia. In a large study that included 733 asymptomatic patients with ESRD, a high percentage of the patients had elevated concentrations of troponin (21). The authors of that study reported cTnT elevations in 82% of cases with a 0.01 ng/ml cutoff. In our study, elevated cTnT was prevalent in 21.3% of patients, and we also observed higher frequencies of elevated cTnT with declining renal function. Therefore, it is plausible that the association between cTnT levels and adverse outcomes is at least partly due to the presence of CKD, which by itself is indicative of an adverse outcome. However, our data reveal that cTnT levels ≥0.01 ng/ml remained an independent predictor of death and amputation even after adjusting for eGFR and other potentially confounding factors.

Only recently were cardiac troponin concentrations identified as a possible risk stratification tool in patients with acute or chronic CLI. Rittoo et al. (13) described a high prevalence of elevated cTnT among 39 patients with acute limb ischemia (44%). The cumulative survival rates after 7 days were 53% for cTnT-positive patients and 100% for cTnT-negative patients. However, the number of patients included in that study was small. A previous investigation of our study group highlighted the fact that an elevated cTnT was predictive of a worse in-hospital outcome in terms of mortality and amputation.

**Figure 4** Cumulative Incidence of Mortality and Amputation Stratified by cTnT Values ≥0.01 ng/ml and cTnT Values <0.01 ng/ml During 1-Year Follow-Up

An elevated cardiac troponin T (cTnT) concentration is associated with a significantly higher mortality and amputation rate (log-rank p < 0.001).

**Table 3** Association Between Cardiac Troponin T and Primary Outcomes Using Cox Proportional Hazards Regression Analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Model</th>
<th>Adjusted HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1</td>
<td>6.36 (3.93–10.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4.64 (2.82–7.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>8.14 (3.77–17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amputation</td>
<td>1</td>
<td>4.75 (2.34–9.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.86 (0.92–3.74)</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3.71 (1.33–10.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>Death or amputation</td>
<td>1</td>
<td>5.90 (3.94–8.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.60 (2.39–5.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6.22 (3.33–11.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HRs and corresponding 95% CIs are from Cox proportional hazard regression analysis. Model 1, adjustment for age and eGFR; Model 2, adjustment for age, eGFR, current smoking, diabetes, and CLI. Model 3 = Model 2 excluding patients with ECG changes suggestive of acute myocardial ischemia.

CLI = critical limb ischemia; ECG = electrocardiographic; eGFR = estimated glomerular filtration rate; other abbreviations as in Table 2.
mortality and amputation (HR: 3.4; 95% CI: 1.3 to 8.5) in patients with acute limb ischemia (HR: 4.2; 95% CI: 1.3 to 12.7). In other investigations, Landesberg et al. (31) and Kertai et al. (32) demonstrated that low levels of asymptomatic troponin elevation during the perioperative period are associated with a poorer long-term outcome in patients undergoing major vascular surgery. To our knowledge, the present study is the first one that evaluated the prognostic value of cTnT in a large cohort of symptomatic PAD patients and provided strong evidence of an independent relationship between cTnT values ≥0.01 ng/ml and an increased mortality and amputation risk.

The mechanisms responsible for the release of cardiac troponin are most likely multifactorial and, in our patients, may include transient, clinically silent myocardial ischemia and small-vessel occlusions, myocardial strain, apoptosis of cardiomyocytes, impaired renal function, and inflammatory processes (33,34). Given the strong relationship between CAD and PAD as clinical manifestations of atherosclerosis, it is very likely that elevations in cTnT can result from transient and less-severe ischemia as a consequence of a mismatch between the oxygen supply and demand, and the exposure of myocardial cells to cytokines.

Furthermore, in the special situation of CLI, the increase in cardiac troponin appeared to be directly associated with skeletal muscle damage and rhabdomyolysis (35–37). It has been suggested that the release of necrotic muscle constituents into the circulation may have direct toxic effects on myocardial cells. However, Jaffe et al. (38) observed an increased cTnT quantified with a fourth-generation cTnT assay in 16 cases with skeletal muscle myopathy. The diagnosis of myopathy had been suggested by clinical history, examination, and increases of the creatine kinase and was confirmed by typical electromyographic changes and skeletal muscle biopsy. These results are in line with a previously published study reporting increased creatine kinase and cTnT, but not cTnI, levels among patients with idiopathic inflammatory myopathies (39). However, this issue of specificity is far from settled. There is some evidence that cTnI is also expressed in myopathic skeletal muscle tissue. Messner et al. (40) studied mRNA expression of cTnT and cTnI in the skeletal muscle and found that the mRNA of both cardiac troponin isoforms was expressed in the skeletal muscles of patients with myopathies (e.g., Duchenne muscular dystrophy). It has been suggested that re-expression of the fetal cTnT isoform in response to injury may contribute to the increase in cTnT levels (38,41). Another study investigated marathon runners and discovered cTnT to be undetectable before the race and to be elevated in 43% of the runners after the race. In this study, the elevations in cTnT were also related to higher inflammation markers (i.e., leukocyte and neutrophil counts, C-reactive protein, interleukin-6) (42).

Study limitations. The present study has some important limitations, which include the selection of patients included in this retrospective trial, the use of a conventional fourth-generation cTnT assay, and the fact that we did not perform serial cTnT testing and ECG recordings. Therefore, we cannot distinguish accurately between elevations due to acute silent myocardial ischemia and chronic disease, which is a major limitation in the interpretation of our results. However, the patients enrolled in this study were admitted to the hospital because of symptomatic PAD for angiography and endovascular revascularization, and they had no symptoms suggestive of ACS. In addition, our findings were not significantly attenuated after exclusion of patients with ECG changes that might be indicative of acute myocardial ischemia.

Previous studies have illustrated the fact that PAD patients have a substantially increased risk of cardiovascular morbidity and mortality (16,43,44). Among patients with symptomatic PAD and without clinical symptoms suggesting myocardial ischemia, an elevated cTnT is detectable in every fifth patient. According to our study, small elevations of cTnT (≥0.01 ng/ml) measured with a conventional cTnT assay predicted a markedly increased risk for death and amputation during the 1-year follow-up. A highly sensitive cTnT assay has recently been developed, allowing for the measurement of concentrations 10-fold lower than those measurable with conventional assays (45). These novel high-sensitivity cTnT assays clearly improve diagnostic performance in terms of an early and reliable diagnosis of acute myocardial infarction and have widely replaced the fourth-generation cTnT assay used in our study. However, the higher sensitivity of these novel assays is counterbalanced by a lower specificity. Thus, some of these assays allow the detection of cTnT even in up to 90% in the general population (45). Despite a number of trials providing evidence for the prognostic impact of higher hs-cTnT levels in patients with stable CAD, ACS, chronic heart failure, and ESRD (2,27,46,47), as well as in the general population (4,10,34), the optimal decision limit for the diagnosis of acute myocardial infarction and the optimal cutoff value for prognostic purposes remain to be determined (48).
Conclusions

Cardiac troponin T is frequently elevated in PAD patients and is associated with higher rates of events such as total mortality and amputation. Even small cTnT elevations predict a markedly increased risk that is independent of impaired renal function. However, further studies are needed to assess the prevalence, determinants, and prognostic implications of cTnT elevations measured by conventional or high-sensitivity assays in PAD patients.

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