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ORIGINAL RESEARCH ARTICLE

Exercise-Induced Cardiac Troponin I Increase and Incident Mortality and Cardiovascular Events

Editorial, see p XXX

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BACKGROUND: Blood concentrations of cardiac troponin above the 99th percentile are a key criterion for the diagnosis of acute myocardial injury and infarction. Troponin concentrations, even below the 99th percentile, predict adverse outcomes in patients and the general population. Elevated troponin concentrations are commonly observed after endurance exercise, but the clinical significance of this increase is unknown. We examined the association between postexercise troponin I concentrations and clinical outcomes in long-distance walkers.

METHODS: We measured cardiac troponin I concentrations in 725 participants (61 [54–69] yrs) before and immediately after 30 to 55 km of walking. We tested for an association between postexercise troponin I concentrations above the 99th percentile (>0.040 μg/L) and a composite end point of all-cause mortality and major adverse cardiovascular events (myocardial infarction, stroke, heart failure, revascularization, or sudden cardiac arrest). Continuous variables were reported as mean ± standard deviation when normally distributed or median [interquartile range] when not normally distributed.

RESULTS: Participants walked 8.3 [7.3–9.3] hours at 68±10% of their maximum heart rate. Baseline troponin I concentrations were >0.040 μg/L in 9 participants (1%). Troponin I concentrations increased after walking (*P*<.001), with 63 participants (9%) demonstrating a postexercise troponin concentration >0.040 μg/L. During 43 [23–77] months of follow-up, 62 participants (9%) experienced an end point; 29 died and 33 had major adverse cardiovascular events. Compared with 7% with postexercise troponin I ≤0.040 μg/L (log-rank *P*<.001), 27% of participants with postexercise troponin I concentrations >0.040 μg/L experienced an end point. The hazard ratio was 2.48 (95% CI, 1.29–4.78) after adjusting for age, sex, cardiovascular risk factors (hypertension, hypercholesterolemia or diabetes mellitus), cardiovascular diseases (myocardial infarction, stroke, or heart failure), and baseline troponin I concentrations.

CONCLUSIONS: Exercise-induced troponin I elevations above the 99th percentile after 30 to 55 km of walking independently predicted higher mortality and cardiovascular events in a cohort of older long-distance walkers. Exercise-induced increases in troponin may not be a benign physiological response to exercise, but an early marker of future mortality and cardiovascular events.

Key Words: cardiovascular diseases ■ death, sudden, cardiac ■ exercise ■ risk factors ■ troponin I ■ walking

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Clinical Perspective

What Is New?

- Postexercise troponin I concentrations above the 99th percentile were found in 9% of the participants, and 27% of those participants died or had major adverse cardiovascular events during follow-up compared with 7% of participants with postexercise troponin I below the 99th percentile.
- Greater exercise-induced changes in troponin I concentrations were associated with lower event-free survival.

What Are the Clinical Implications?

- The present study suggests that exercise-induced increase in troponin may not be a benign physiological response to exercise, but an early marker of future mortality and cardiovascular events.
- Higher concentrations of postexercise troponin may represent myocardial injury because of underlying, subclinical, cardiac pathology.

Cardiac troponin is a protein that facilitates cardiomyocyte contraction. Dynamic changes in circulating troponin concentrations with at least 1 value exceeding the 99th percentile (the upper reference limit [URL]) in a clinical setting consistent with myocardial ischemia, are used to diagnose myocardial infarction, whereas a value above the URL alone indicates myocardial injury.[1] Even cardiac troponin values below the URL are associated with increased mortality and cardiovascular disease (CVD) morbidity in the general[2] and patient population.[3–5]

Physical activity and exercise are associated with significant reductions in cardiovascular events[6,7] and with increased longevity.[8,9] Paradoxically, multiple studies have shown that exercise acutely increases troponin concentrations,[10] after a brief or long exercise duration, performed at either moderate or high-intensity.[10,11] Such exercise-induced increases in troponin concentrations are considered benign because they occur frequently, are present in (apparently) healthy individuals, and are not accompanied by clinical symptoms. Nevertheless, the mechanisms and clinical significance of exercise-induced increases in troponin are incompletely understood.[11,12] We examined the association between postexercise troponin concentrations above the URL and clinical outcomes in a heterogeneous cohort of older long-distance walkers. We also identified participant and exercise characteristics associated with postexercise troponin concentrations above the URL.

METHODS

Study Population

The Nijmegen Four Days Marches is the largest walking event in the world (http://www.4daagse.nl/en/). Marchers in the 2008 to 2016 events were recruited by social media and website advertisement. Participants in the Nijmegen Marches walked 30, 40, 50, or 55 km per day, depending on age and sex, for 4 consecutive days. For this study, we only performed measurements on the first walking day. Participants self-selected their pace and rest times. Subjects completed a questionnaire about their cardiovascular health status and prescribed medications. This information was used to categorize individuals as participants with CVD (defined as a diagnosis of myocardial infarction, stroke, or heart failure), participants with cardiovascular risk factors ([CVRF] defined as treated hypertension, hypercholesterolemia, or diabetes mellitus), or participants without CVD and CVRF at baseline (controls). Participants provided written informed consent. The medical ethical committee of the Radboud University Medical Center approved the study (NL18245.091.07). The study was conducted in accordance with the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Procedures

One or 2 days before the event (ie, baseline), body mass (Seca 888 Scale; Seca, Hamburg, Germany) and height were measured. Body mass was also measured directly before and after walking to provide a surrogate of change in hydration status.[13] A venous blood sample (10 mL) was drawn from an antecubital vein at baseline and ~10 minutes after the finish of the first walking day (postexercise). Blood samples were collected in serum-gel Vacutainer tubes and allowed to clot for ~45 minutes. After centrifugation, serum was aliquoted, frozen (all directly done on-site), and stored at –80°C for later analysis (after serum from the last finisher was collected). Troponin concentrations were analyzed using a contemporary troponin I assay (ADVIA Centaur TnI-Ultra; Siemens Healthcare Diagnostics, The Hague, The Netherlands) with an established URL of 0.040 μg/L according to the manufacturer. The coefficient of variation is 8.8% at the URL and 10% at 0.030 μg/L. The analytical limit of detection is 0.006 μg/L. The assay does report values <0.006 μg/L and these values were used to adjust for baseline troponin concentrations in the multivariable analyses.

Start and finish times were used to determine exercise duration and calculate walking speed. Heart rate was recorded every 5 km along the route using a 2-channel electrocardiographic chest band (Polar Electro Oy; Kempele, Finland). Exercise intensity was calculated as average heart rate during exercise divided by estimated maximum heart rate (208–0.7 × age).[14] AQ4

Clinical Outcomes

The primary study end point was a composite of all-cause mortality and major adverse cardiovascular events (MACE). Survival status of study participants was retrieved from the Dutch population register. The final survival assessment was performed on December 13, 2018, ~6 months after the latest annual questionnaire (July 2018) to ensure that those individuals who did not complete the questionnaires had not died. Information about MACEs were collected from annual questionnaires sent to study participants and were defined as myocardial infarction, stroke, heart failure, revascularization (both acute and elective), or sudden cardiac arrest during

follow-up. We evaluated medication use to ensure it matched the reported diagnoses. For the primary end point, participants were followed until first MACE or death, and those without an end point were censored on the date of the last completed questionnaire. Secondary end points were the individual components of the composite end point, all-cause mortality, with follow-up until date of death or final survival assessment (regardless of the date of the last completed questionnaire), and MACE, with follow-up until date of first event or last completed questionnaire.

Statistical Analysis

All variables were visually inspected for normality and checked for kurtosis and skewness. Continuous variables were reported as mean±SD when normally distributed or median [interquartile range] when not normally distributed and categorical variables were presented as proportions. Depending on whether data were normally distributed, *t* tests or Mann–Whitney *U* tests were used to compare continuous variables. Pearson Chi-Square tests were used to compare categorical variables.

Kaplan–Meier curves were generated to evaluate and depict unadjusted survival plots of the composite end point of all-cause mortality and MACE for postexercise troponin concentrations >0.040 μg/L and ≤0.040 μg/L. Similar procedures were performed for the secondary end points, the individual components mortality and MACE. Cox proportional-hazards regression analyses were performed to calculate unadjusted and adjusted hazard ratios for primary and secondary end points. First, univariable Cox regression analysis of participant characteristics were used to identify potential confounders of the association between postexercise troponin I and clinical outcomes. Variables that were associated (P<0.10) with the primary end point were included in a multivariable analysis. We included postexercise troponin I and the potential confounders, and subsequently removed variables with a P>0.10 association following a stepwise approach. Remaining variables were included in the multivariable-adjusted model. Sensitivity analyses were performed to evaluate the robustness of our findings. To ensure that the results were not attributable to including individuals with CVD, stratified analyses were performed in individuals without CVD at baseline. Additionally, explorative analyses were performed to investigate whether detectable troponin I concentrations below the URL were associated with the primary and secondary end points by performing the analyses for 3 groups of postexercise troponin I concentrations: <0.006, 0.006 to 0.040, and >0.040 μg/L. Moreover, Kaplan–Meier curves and Cox proportional-hazards models were generated to investigate the association between delta (postexercise minus baseline) troponin I concentrations (>0.010, >0.020, >0.030, and >0.040 μg/L) and the primary and secondary end points.

Binary logistic regression was used to calculate unadjusted and multivariable adjusted odds ratios for the association between participant and exercise characteristics and postexercise troponin I values above the URL. First, univariable logistic regression analysis of variables was used to select potential predictors for multivariable analysis. Variables that were associated (P<0.10) with postexercise troponin I values above the URL were subsequently included in a multivariable backward logistic regression analysis to gain insight into which variables could independently predict postexercise troponin I concentrations >0.040 μg/L.

All statistical analyses were performed using SPSS Statistics 24 (SPSS, Inc., Chicago, Illinois). Statistical significance was assumed at P<0.05.

RESULTS

A total of 804 participants were recruited (Figure 1). Seventy-nine individuals who were alive at the end of follow-up declined to complete the additional annual questionnaires on cardiovascular events. Therefore, 725 participants were included in the analyses of the primary composite end point of all-cause mortality and MACE (Table 1). Participants were 61 [54–69] years old at baseline and 62% were male (Table 1). A total of 14% had CVD, 26% had only CVRF, and 60% had no CVD or CVRF at baseline (controls). For the primary composite end point, participants had a median follow-up of 43 [23–77] months. The total cohort of 804 participants was included in the analyses of only all-cause mortality as a secondary end point (52 [28–100] months follow-up). Eleven participants died before completion of the first questionnaire for assessment of MACE, thus 714 participants were included in the analyses of the secondary end point of only MACE (43 [23–77] months follow-up).

Exercise Characteristics and Troponin

Participants walked 8.3 [7.3–9.3] hours at 68±10% of their predicted maximum heart rate. Baseline troponin I concentrations were detectable (≥0.006 μg/L) in 233 (33%) participants, with 9 participants (1%) demonstrating a value >0.040 μg/L. At baseline, participants with CVD had detectable troponin concentrations more frequently than those with CVRF, who had detectable troponin concentrations more frequently than controls. Frequency of troponin concentrations >0.040 μg/L did not differ between groups at baseline (Figure 2). Troponin concentrations increased after exercise (P<0.001) and 418 participants (58%) had detectable troponin concentrations, with 63 participants (9%) demonstrating a value >0.040 μg/L. Postexercise, troponin concentrations increased in all groups (P<0.001) and were more frequently detectable in participants with CVD and CVRF, and more often >0.040 μg/L in those with CVD compared with controls (Figure 2).

Clinical Outcomes

During follow-up, 62 participants reached the primary end point: 29 died and 33 had MACE. First MACE during follow-up included 6 myocardial infarctions (18%), 17 strokes (52%), 4 heart failure diagnoses (12%), 5 revascularizations (15%), and 1 resuscitated sudden

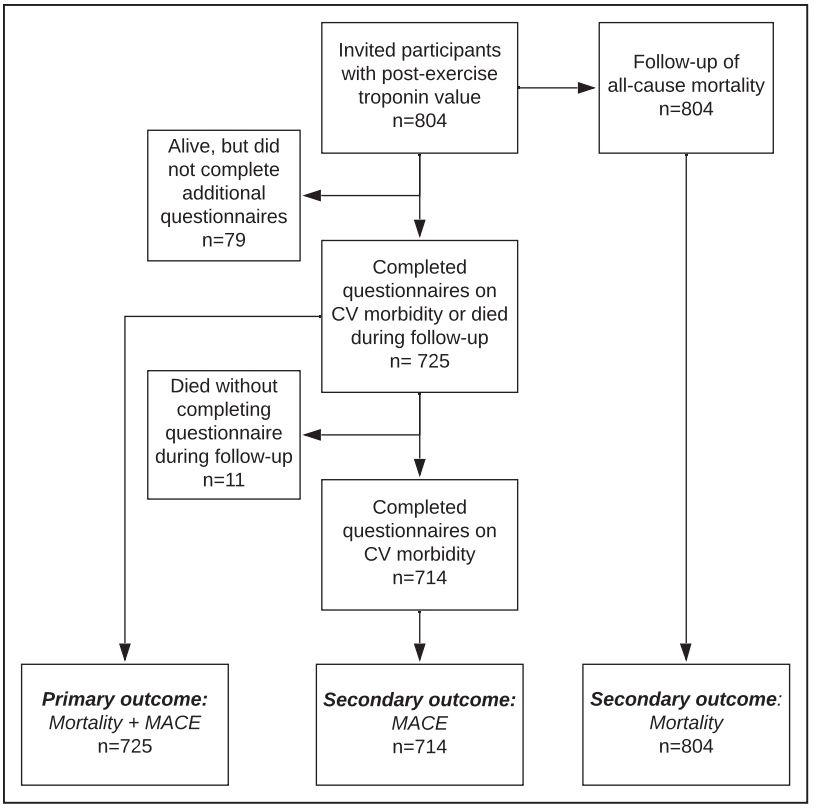

Figure 1. Flowchart of study procedures.

cardiac arrest (3%). Twenty-one participants with CVD (20%) died or had MACE, compared with 24 (13%) with CVRF and 17 (4%) controls (P<0.001). A total of 27% of the participants with postexercise troponin >0.040 μg/L died or had MACE, compared with 7% of those with a concentration ≤0.040 μg/L. Unadjusted Kaplan–Meier analyses revealed a significantly lower event-free survival among participants who had postexercise troponin I >0.040 μg/L compared with those ≤0.040 μg/L (P<0.001; Figure 3). Similar results were observed for the secondary end points of all-cause mortality (Figure I in the online-only Data Supplement) and MACE (Figure II in the online-only Data Supplement).

Cox proportional-hazards models showed associations between the primary end point and the following variables: baseline troponin, postexercise troponin, age, sex, body mass index, presence of CVRF and CVD, and smoking (Table I in the online-only Data Supplement). After multivariable adjustment, baseline and postexercise troponin, age, sex, and presence of CVD and CVRF remained independently associated with the primary end point (Table I in the online-only Data Supplement). Similar Cox proportional-hazards models were made for the secondary end points mortality (Table II in the online-only Data Supplement) and MACE (Table III in the online-only Data Supplement). The crude hazard ratio of postexercise troponin I >0.040 μg/L with all-cause mortality and MACE was 5.21 (95% CI, 2.96–9.17). After adjustment for age, sex, and presence of CVD and CVRF, the hazard ratio was 3.21 (95% CI, 1.79–5.77), which further decreased to 2.48 (95% CI, 1.29–4.78) after additional adjustment for baseline troponin (Table 2). Associations between postexercise troponin >0.040 μg/L and the individual components of the primary end point were stronger for MACE compared with all-cause mortality (Table 2).

Sensitivity analyses, excluding individuals with CVD at baseline, further reinforced our findings. Of the participants without CVD at baseline, 26% of those with postexercise troponin I >0.040 μg/L died or had MACE, compared with 5% of those with troponin ≤0.040 μg/L. Unadjusted Kaplan–Meier analyses revealed a significantly lower event-free survival among participants who had postexercise troponin >0.040 μg/L compared with those ≤0.040 μg/L (p<.001, Figure III in the online-only Data Supplement). The adjusted hazard ratio for postexercise troponin I >0.040 μg/L was 3.28 (95% CI, 1.48–7.29) for all-cause mortality and MACE, 0.51 (95% CI, 0.10–2.52) for all-cause mortality, and 7.42 (95% CI, 2.57–21.37) for MACE (Table IV in the online-only Data Supplement).

Exploratory analyses of postexercise troponin I concentrations <0.006, 0.006 to 0.040, and >0.040 μg/L suggested that the risk for individuals with postexercise troponin I concentrations 0.006 to 0.040 μg/L did not differ from those with postexercise troponin I <0.006 μg/L (Figure IV and Table V in the online-only Data Supplement). Kaplan–Meier curves and Cox regression analyses of delta troponin concentrations demonstrated a lower event-free survival for participants with higher delta troponin concentrations and hazard ratios

Table 1. Participant and Exercise Characteristics, Total and Split, for Cardiac Troponin I Below and Above the Upper Reference Limit

Participant and Exercise Characteristics	Total	Postexercise Troponin I ≤0.040 μg/L	Postexercise Troponin I >0.040 μg/L	*P* Value
N	725	662	63	
Age, y	61.4 [54.4–69.1]	61.1 [54.1–68.3]	66.4 [60.0–81.3]	<0.001
Sex, n (%)				<0.001
Male	446 (62)	393 (59)	53 (84)	
Female	279 (38)	269 (41)	10 (16)	
Height, m	1.73 (0.09)	1.73 (0.09)	1.75 (0.07)	0.10
Body mass, kg	79.1 (14.5)	78.6 (14.5)	83.8 (14.0)	0.01
Body mass index, kg/m^2	26.2 (3.6)	26.1 (3.6)	27.2 (3.7)	0.01
Smoking, n (%)				0.79
Never	289 (41)	266 (42)	23 (37)	
Current smoking	30 (4)	27 (4)	3 (5)	
Previously smoked	383 (55)	347 (54)	36 (58)	
Cardiovascular risk factors, n (%)	258 (36)*	224 (34)	34 (54)	0.002
Hypertension	173 (24)	145 (22)	28 (44)	<0.001
Hypercholesterolemia	106 (15)	90 (14)	16 (25)	0.02
Diabetes mellitus	64 (9)	56 (8)	8 (13)	0.37
Cardiovascular diseases, n (%)	104 (14)	87 (13)	17 (27)	0.005
Myocardial infarction	65 (9)	54 (8)	11 (18)	0.03
Stroke	26 (4)	22 (3)	4 (6)	0.38
Heart failure	33 (5)	27 (4)	6 (10)	0.10
Baseline troponin I, n (%)				<0.001
≥0.006–0.040 μg/L	224 (31)	191 (30)	33 (53)	
>0.040 μg/L	9 (1)	3 (1)	6 (10)	
Walking distance, n (%)				0.18
30 km	324 (45)	289 (44)	35 (56)	
40 km	300 (41)	278 (42)	22 (35)	
50 or 55 km	101 (14)	95 (14)	6 (10)	
Walking duration, h	8.3 [7.3–9.3]	8.3 [7.4–9.3]	8.3 [6.9–9.0]	0.25
Walking speed, km/h	4.4 [4.0–4.9]	4.4 [4.0–4.9]	4.3 [3.7–5.0]	0.52
Exercise intensity, %	67.8 (10.3)	67.5 (9.9)	71.2 (13.0)	0.01
Change in body mass, %	−1.0 (1.0)	−1.0 (1.0)	−1.3 (0.9)	0.02
Postexercise troponin I, n (%)				<0.001
≥0.006–0.040 μg/L	355 (49)	355 (54)	0 (0)	
>0.040 μg/L	63 (9)	0 (0)	63 (100)	

Body mass index = body mass/length^2.Exercise intensity = average heart rate/maximum estimated heart rate. Continuous variables were reported as mean (SD) when normally distributed or median [interquartile range] when not normally distributed.

*Note that this group contains individuals with only cardiovascular risk factors (26%) and cardiovascular disease with cardiovascular risk factors (10%).

increased when using higher cut-off values for Δ troponin concentrations (Figure 4, Table 3).

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Factors Associated With Postexercise Troponin

Of the total cohort of 804 participants, 72 participants had postexercise troponin I values >0.040 μg/L and those individuals were older, more often male, heavier, more often had CVD and CVRF, had higher baseline troponin values, walked at a higher exercise intensity, and lost more body mass during walking (Table VI in the online-only Data Supplement). These findings were confirmed by logistic regression analysis (Table VII in the online-only Data Supplement) as age (odds ratio, 1.07; 95% CI, 1.04–1.10), body mass (odds ratio, 1.04; 95%

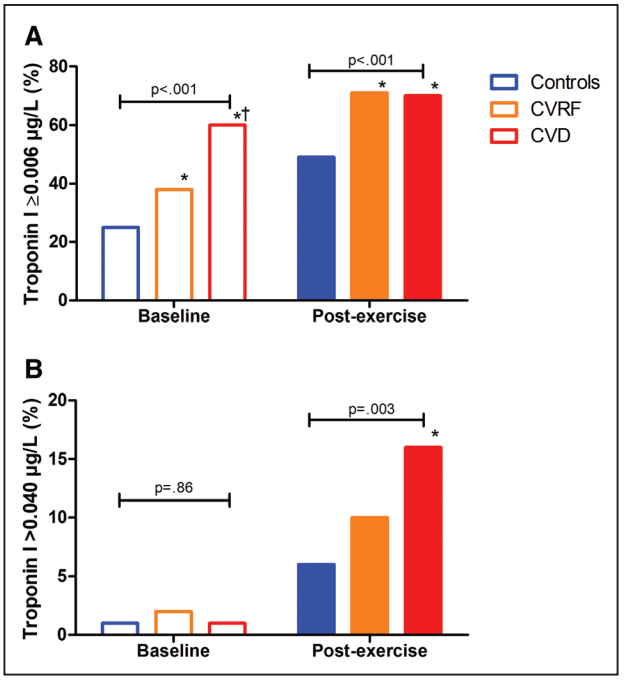

Figure 2. Prevalence of baseline and postexercise cardiac troponin I values above the limit of detection (≥0.006 µg/L) and upper reference limit (>0.040 µg/L) across cardiovascular health groups.
At baseline, participants with cardiovascular diseases (CVD) more frequently had detectable (≥0.006 µg/L) troponin I concentrations compared with those with risk factors (CVRF), who more frequently had detectable troponin concentrations than participants without CVD and CVRF at baseline (controls). Postexercise troponin I concentrations were more frequently detectable in participants with CVD and CVRF compared with controls (**A**). At baseline, troponin I concentrations >0.040 µg/L were rare and did not differ across groups. Participants with CVD more often had postexercise values >0.040 µg/L compared with controls (**B**). **P*<0.05 compared with controls; †*P*<0.05 compared with CVRF.

CI, 1.02–1.07), baseline troponin (odds ratio, 1.08; 95% CI, 1.05–1.11), exercise intensity (odds ratio, 1.05; 95% CI, 1.02–1.08), and change in body mass during exercise (odds ratio, 0.69; 95% CI, 0.50–0.94) were independently associated with postexercise troponin I >0.040 µg/L (full model R^2=0.32; Table VII in the online-only Data Supplement).

DISCUSSION

Elevated troponin concentrations are frequently observed after exercise of varying duration and intensity. This exercise-associated elevation has commonly been considered to represent a benign phenomenon[11,12]. We examined the potential clinical relevance of exercise-induced troponin elevations and found that postexercise troponin I concentrations above the URL after recreational walking exercise were associated with a lower event-free survival. This association was independent of age, sex, presence of CVD and CVRF, and baseline troponin concentrations. The occurrence of postexercise troponin I >0.040 µg/L was directly associated with age, body mass, exercise intensity, loss of body mass during exercise, and baseline troponin concentrations. These findings indicate that postexercise troponin I concentrations above the URL may be a marker of future mortality and cardiovascular events.

Troponin and Clinical Outcomes

With the exception of exercise-induced troponin increase, troponin elevation is associated with increased risks for mortality and cardiovascular morbidity.[2–5] We found that a greater exercise-induced troponin I release and postexercise troponin I concentrations above the URL are also associated with a higher incidence of mortality and cardiovascular events during follow-up. Importantly, this association remained significant even after adjusting for baseline values. This observation suggests that exercise-induced troponin concentrations provide prognostic information beyond that of baseline troponin. Higher concentrations

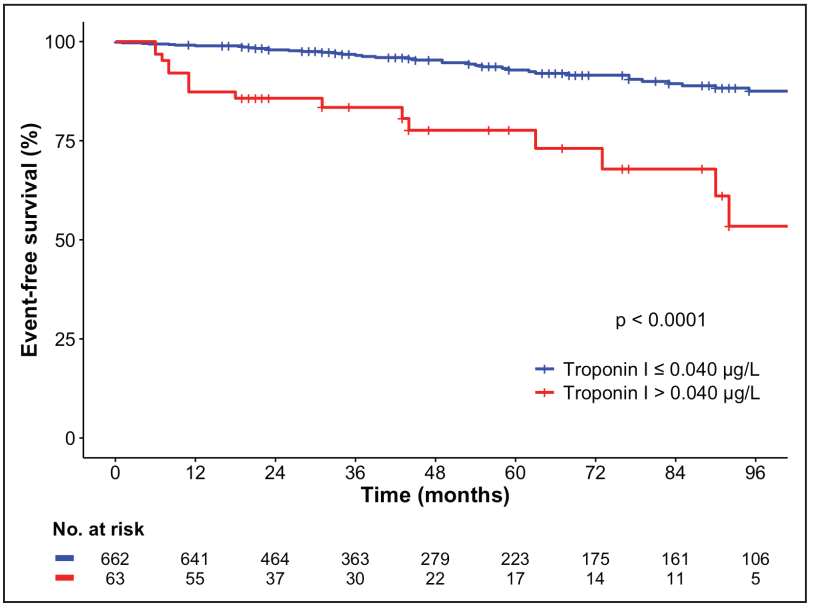

Figure 3. Unadjusted Kaplan–Meier estimates of all-cause mortality and major adverse cardiovascular events during follow-up.
Participants with exercise-induced cardiac troponin I concentrations above the upper reference limit (>0.040 µg/L) had a significantly lower event-free survival compared with those below the upper reference limit (≤0.040 µg/L).

Table 2. Unadjusted and Multivariable-Adjusted Associations Between Postexercise Troponin I Concentrations Above the Upper Reference Limit (>0.040 μg/L) and Incidence of All-Cause Mortality and Major Adverse Cardiovascular Events, and Mortality and Major Adverse Cardiovascular Events Individually

	Unadjusted		Model 1*		Model 2†	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Mortality and MACE	N=725		N=725		N=701	
Postexercise troponin I >0.040 μg/L	5.21 (2.96–9.17)	<0.001	3.21 (1.79–5.77)	<0.001	2.48 (1.29–4.78)	0.01
Mortality	N=804		N=793		N=764	
Postexercise troponin I >0.040 μg/L	2.92 (1.19–7.19)	0.02	1.44 (0.56–3.70)	0.44	1.09 (0.38–3.10)	0.88
MACE	N=714		N=714		N=690	
Postexercise troponin I >0.040 μg/L	7.09 (3.89–14.86)	<0.001	4.82 (2.24–10.37)	<0.001	3.75 (1.56–9.02)	0.003

MACE were myocardial infarction, stroke, heart failure, aborted cardiac arrest, or revascularization. CI indicates confidence interval; and MACE, major adverse cardiovascular events.

*Adjusted for age, sex, baseline cardiovascular diseases, and cardiovascular risk factors.

†Adjusted for model 1 and for baseline troponin I concentrations (continuous variable). Some study participants had missing data of confounding factors, so n=11 (model 1) and n=29 (model 2) were excluded from the adjusted Mortality analyses, whereas n=24 (model 2) were excluded from the Mortality and MACE and MACE analyses.

of postexercise troponin may represent myocardial injury because of underlying, subclinical, cardiac pathology. This hypothesis is supported by our finding of a higher incidence of postexercise troponin >0.040 μg/L in participants with CVD, but also the stronger association between postexercise troponin >0.040 μg/L and MACE versus mortality. Exposure of individuals to bouts of exercise can unmask myocardial vulnerability,[15] which would remain unnoticed under resting conditions. Patients with coronary artery disease and exercise-induced myocardial ischemia may have higher postexercise troponin I concentrations than those without ischemia.[16] Moreover, a recent pilot study reported that high postexercise troponin I concentrations were associated with occult coronary artery disease in recreational cyclists.[17] Möhlenkamp et al found higher postexercise troponin I concentrations in marathon runners with myocardial late gadolinium enhancement.[18] These findings suggest that postexercise troponin I concentrations above the URL could indicate the presence of underlying (subclinical) cardiac disease.

Alternatively, exercise-induced troponin elevations could also represent acute myocardial injury, independent of myocardial vulnerability. This interpretation fits with the ongoing question as to whether high-volume high-intensity exercise training may cause detrimental cardiac adaptions.[10,19] A higher prevalence of coronary atherosclerosis,[20] myocardial fibrosis,[21] and atrial fibrillation[22] have been reported in amateur athletes reporting a large lifelong exercise volume. Long-term, high-volume exercise could produce repetitive myocardial injury leading to these cardiac maladaptations. Additional studies are necessary to test this hypothesis.

Potential Mechanisms of Troponin Release

We found that age, body mass, baseline troponin, exercise intensity, and change in body mass during exercise were independently associated with a postexercise troponin I >0.040 μg/L. There are 5 proposed mechanisms of exercise-induced troponin release into the bloodstream: (1) myocyte necrosis, (2) apoptosis, (3) cellular release of troponin degradation products, (4) increased cellular membrane permeability, and (5) release of membranous blebs.[11,23,24] Myocyte necrosis and apoptosis represent irreversible myocardial injury, whereas the other mechanisms are characterized by reversible cardiomyocyte damage.[12] Postexercise troponin T concentrations in marathon runners are composed of small, degraded, T molecules.[25] This observation supports the hypothesis that exercise induces reversible myocardial injury, allowing degraded troponin molecules to exit the cardiomyocyte. For example, increases in preload can cause troponin degradation[26] and small troponin fragments could pass through a cellular membrane with normal membrane integrity.[23] Alternatively, exercise could increase membrane permeability by stimulating stretch-responsive integrins[27] or by causing cell "wounds" (ie, transient disruptions of the membrane),[28] allowing intact[27] or degraded[26] troponin fragments to enter the bloodstream. The frequency at which these wounds occur increases with higher heart rate and contractility, and may contribute to myocyte hypertrophy.[28] Our finding that a higher exercise intensity was independently associated with an increased prevalence of troponin I above the URL supports the hypothesis that exercise may induce transient troponin elevations attributable to transient increases in cardiomyocyte membrane permeability.

Clinical Relevance

We demonstrated that the prevalence of troponin I concentrations >0.040 μg/L increased from 1% at baseline to 9% postexercise, and that postexercise troponin I concentrations >0.040 μg/L were associated with future mortality and MACE. Our sensitivity analyses further confirmed the outcomes of our

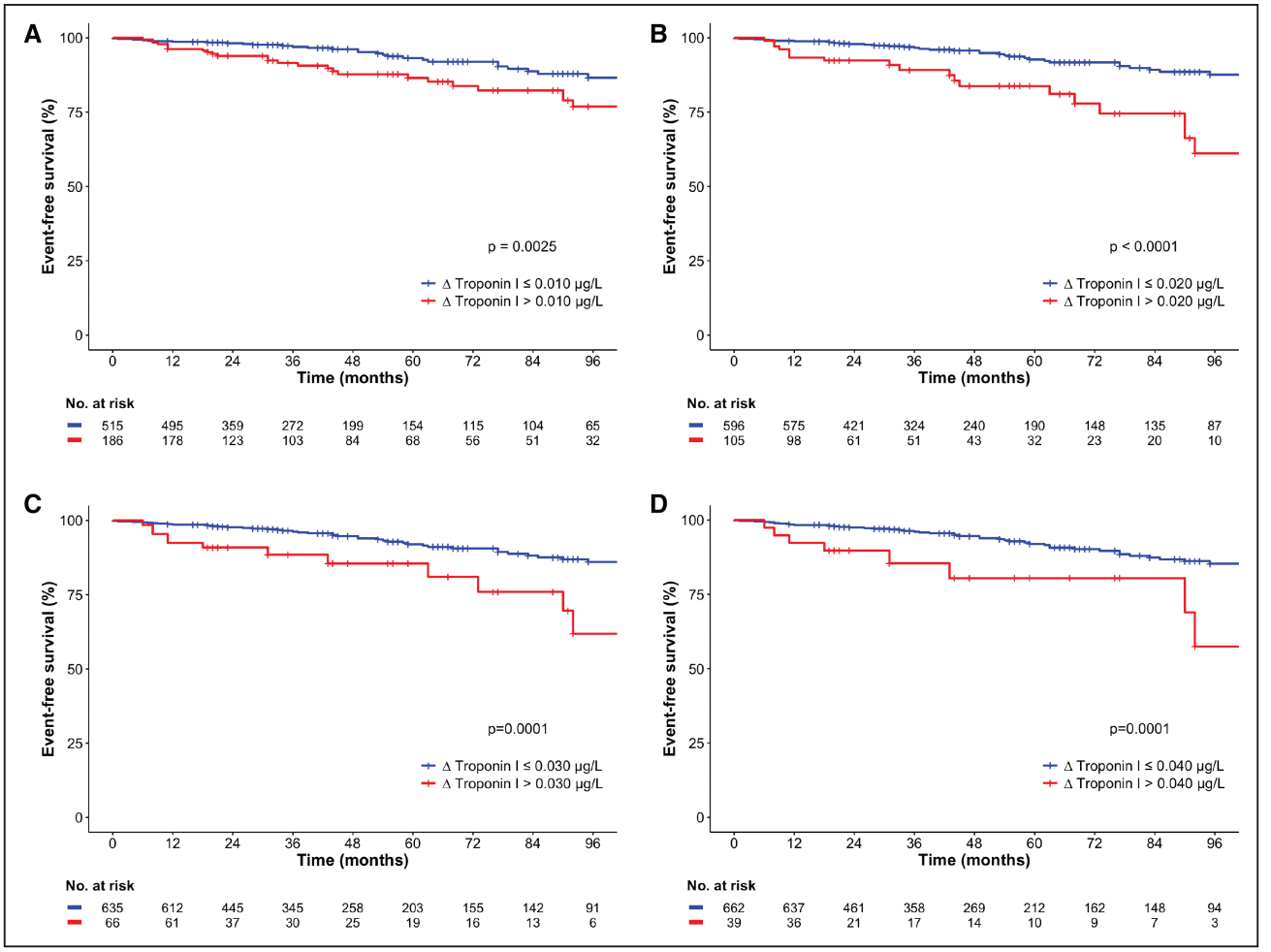

Figure 4. Unadjusted Kaplan–Meier estimates of all-cause mortality and major adverse cardiovascular events during follow-up.
Participants with Δ (postexercise minus baseline) cardiac troponin I concentrations >0.010 µg/L (**A**), >0.020 µg/L (**B**), >0.030 µg/L (**C**), and >0.040 µg/L (**D**).

study, as we found that the association between postexercise troponin >0.040 µg/L and mortality and MACE was even stronger in participants without CVD at baseline. These findings suggest that exercise-induced troponin I is an independent marker of future mortality and MACE among individuals with and without CVD.

The incidence of exercise-induced troponin I concentrations above the URL was relatively low (9%) in our study of long-distance walkers. Studies in marathon runners have reported that >50% of runners have postexercise troponin concentrations above the URL[29–31] and it is not clear whether such a high prevalence of exercise-induced troponin increases has similar clinical predictive value. Möhlenkamp et al evaluated 6-year coronary event rates between marathon runners with postexercise cardiac troponin I above and below the median and found no differences in their cohort, but they followed only 74 marathon runners of whom 6 had an event.[18] Consequently, additional studies are needed to confirm our observation in different populations with different exercise exposures.

It is currently unclear how these findings impact troponin testing before and after clinical stress testing. A recent meta-analysis found no difference in poststress (either bicycle exercise or pharmacological test) troponin concentrations in individuals with inducible or noninducible myocardial ischemia.[32] However, only a nonsignificant 0 to 2 ng/L change in troponin concentrations was found, suggesting that the exercise intensity may not have been sufficiently high to maximally stress the heart and identify individuals at risk. Furthermore, postexercise troponin concentrations were not evaluated as above versus below the URL. Also, troponin release may not be solely attributable to myocardial ischemia. Thus, additional studies are needed to evaluate our observation in the setting of clinical stress/exercise testing and whether measurement of cardiac troponin concentrations provides additional prognostic information.

Limitations

The main limitation of our study is that troponin I was measured using a contemporary assay. High-sensitive

Table 3. Unadjusted and Multivariable-Adjusted Associations between Δ Troponin I Concentrations and Incidence of All-Cause Mortality and Major Adverse Cardiovascular Events, and Mortality and Cardiovascular Events Individually

	Unadjusted		Model 1*		Model 2†	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Mortality and MACE	N=701		N=701		N=701	
Delta troponin I >0.010 µg/L	2.15 (1.29–3.58)	0.003	1.47 (0.87–2.48)	0.15	1.52 (0.90–2.55)	0.12
Delta troponin I >0.020 µg/L	3.31 (1.93–5.69)	<0.001	1.98 (1.13–3.46)	0.02	1.92 (1.10–3.43)	0.02
Delta troponin I >0.030 µg/L	3.18 (1.72–5.91)	<0.001	2.02 (1.08–3.80)	0.03	1.74 (0.92–3.27)	0.09
Delta troponin I >0.040 µg/L	3.71 (1.82–7.58)	<0.001	2.33 (1.12–4.83)	0.02	2.10 (1.01–4.35)	0.047
Mortality	N=773		N=764		N=764	
Delta troponin I >0.010 µg/L	2.86 (1.37–5.95)	0.005	1.80 (0.84–3.86)	0.13	1.78 (0.83–3.80)	0.14
Delta troponin I >0.020 µg/L	2.57 (1.17–5.64)	0.02	1.31 (0.57–3.02)	0.52	1.25 (0.54–2.87)	0.61
Delta troponin I >0.030 µg/L	1.55 (0.54–4.45)	0.42	0.81 (0.27–2.40)	0.70	0.71 (0.24–2.12)	0.54
Delta troponin I >0.040 µg/L	1.95 (0.59–6.43)	0.28	0.94 (0.28–3.22)	0.93	0.83 (0.24–2.87)	0.77
MACE	N=690		N=690		N=690	
Delta troponin I >0.010 µg/L	1.61 (0.78–3.31)	0.20	1.16 (0.55–2.42)	0.70	1.14 (0.54–2.38)	0.73
Delta troponin I >0.020 µg/L	3.72 (1.78–7.81)	0.001	2.55 (1.19–5.46)	0.02	2.24 (1.04–4.82)	0.04
Delta troponin I >0.030 µg/L	4.78 (2.19–10.45)	<0.001	3.15 (1.42–6.96)	0.005	2.48 (1.09–5.64)	0.03
Delta troponin I >0.040 µg/L	5.18 (2.11–12.75)	<0.001	3.76 (1.50–9.45)	0.005	2.78 (1.07–7.26)	0.04

MACE were myocardial infarction, stroke, heart failure, aborted cardiac arrest, or revascularization. Δ indicates postexercise minus baseline troponin concentration. CI indicates confidence interval; and MACE, major adverse cardiovascular events.

*Adjusted for age, sex, baseline cardiovascular diseases and cardiovascular risk factors.

†Adjusted for model 1 and for baseline troponin I concentrations (continuous variable). Some study participants had missing data of baseline troponin concentrations and confounding factors, so n=24 were excluded from Mortality and MACE and MACE analyses, whereas n=31 (unadjusted) and n=9 (model 1) were excluded from Mortality analyses.

assays are capable of measuring troponin concentrations in more than 50% of healthy individuals, but it is important to emphasize that the coefficient of variation at the URL is comparable for our contemporary assay and other the high-sensitive assays (8.8% versus 5–10%).[33] Nevertheless, we cannot predict how the use of a high-sensitive assays would affect our results.

Our study is also limited by sample size, a relatively short duration of follow-up and a low event rate. Nevertheless, this is the largest study to investigate clinical outcomes of exercise-induced troponin elevations. Another limitation is that we used questionnaires to record cardiovascular morbidity. However, we evaluated medication use to cross-validate the self-reported diagnoses. Findings from this study cannot be directly extrapolated to other populations and/or other types of exercise. Higher-volume, higher-intensity exercise produces a higher prevalence of postexercise troponin concentrations above the URL. Individuals able to engage in such intense exercise and their CVD outcomes are likely to be different from the older long-distance walkers that we studied. Training experience can affect the exercise-induced troponin response[34,35] and is potentially associated with clinical outcomes, but we did not have detailed training records for our participants. However, training experience may also be a surrogate for exercise intensity and/or duration and although we found that exercise intensity was significantly associated with troponin I concentrations above the URL, it was not significantly associated with clinical outcomes in the univariate Cox regression analysis.

Conclusions

Older long-distance walkers with exercise-induced troponin I elevations above the URL after 30 to 55 km of walking exercise had a lower event-free survival and this association was independent of age, sex, presence of CVD and CVRF, and baseline troponin concentrations. These findings suggest that postexercise troponin concentrations above the URL may be an independent marker of future mortality and cardiovascular events, even in individuals without established CVD.

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ORIGINAL RESEARCH ARTICLE

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