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ORIGINAL RESEARCH

Dynamic Changes in High-Sensitivity Cardiac Troponin I Levels Associate With Variations in Cardiovascular Risk Scores in the General Population

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BACKGROUND: In the general population, elevated hs-cTnI (high-sensitivity cardiac troponin I) levels are linked to adverse cardiovascular outcomes. Whether changes in hs-cTnI within the normal range are associated with variations in cardiovascular risk scores remains unclear.

METHODS: This observational substudy of the CV-PREVITAL (Strategies for Primary Cardiovascular Prevention in the Italian Population) project evaluated 810 subjects (522 women) in primary prevention. Hs-cTnI was measured at baseline and after 12 months in 473 participants. Cardiovascular risk was assessed using validated scores along with diet adherence and sleep quality. Clinical and laboratory parameters were recorded. Participants received structured lifestyle counseling.

RESULTS: At baseline, hs-cTnI was undetectable in 59% of participants. Detectable hs-cTnI was associated with older age (58 versus 55 years), higher body mass index (26 versus 24 kg/m^2), greater waist circumference (91 versus 85 cm), higher blood pressure (129 versus 123 mm Hg), lower high-density lipoprotein cholesterol (56 versus 59 mg/dL), higher glycated hemoglobin (40 versus 38 mmol/mol), all $P<0.01$. Progetto Cuore, Framingham Risk Score, Atherosclerotic Cardiovascular Disease, and Finnish Diabetes Risk scores were higher (all $P<0.0001$) in participants with detectable hs-cTnI, whereas the Moli-sani risk score did not differ. At 12 months, participants with undetectable hs-cTnI increased to 79% ($P<0.0001$). Although all scores but 1 improved at follow-up, changes in hs-cTnI were not consistently associated with changes in risk scores or therapy modifications in exploratory analyses.

CONCLUSIONS: In this primary-prevention cohort, the presence of detectable hs-cTnI was associated with a less favorable risk profile. However, its usefulness in the longitudinal monitoring of cardiovascular risk changes requires validation against cardiovascular outcomes.

Key Words: biomarkers ■ cardiovascular risk ■ high-sensitivity cardiac troponin I ■ lifestyle intervention ■ primary prevention

Cardiovascular disease (CVD) prevention has become a priority for health care systems. A healthy lifestyle, including balanced nutrition and regular physical activity, is of paramount importance for maintaining cardiovascular physiology throughout life. According to the World Health Organization, most cardiovascular diseases can be prevented by addressing behavioral and environmental risk factors.[1] On this basis, the CV-PREVITAL (Strategies for Primary Cardiovascular Prevention in the Italian Population)

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CLINICAL PERSPECTIVE

What Is New?

- Detectable hs-cTnI (high-sensitivity cardiac troponin I), even within the normal range, identified participants with a less favorable cardiovascular risk profile at both visits.
- Over 12 months, undetectable hs-cTnI became more frequent, whereas several cardiovascular risk scores improved after counseling and therapy review.

What Are the Clinical Implications?

- Serial hs-cTnI measurement merits further evaluation as a candidate monitoring tool during prevention, pending validation against adjudicated cardiovascular outcomes at follow-up.

Nonstandard Abbreviations and Acronyms

CV-PREVITAL	Strategies for Primary Cardiovascular Prevention in the Italian Population
FINDRISC	Finnish Diabetes Risk Score
Moli-sani	Moli-sani study cohort from the Molise region and associated risk score
Predimed	Prevention With Mediterranean Diet
PSQI	Pittsburgh Sleep Quality Index

project was designed to compare the effectiveness of an educational and motivational mobile health intervention as a tool to reduce cardiovascular risk in the Italian population aged ≥45 years and free from major cardiovascular events.[2] Within this framework, a single-center ancillary study was conducted to investigate the potential of hs-cTnI (high-sensitivity cardiac troponin I) as an additional tool for identifying individuals at increased risk of adverse cardiovascular events.

Beyond acute coronary syndromes,[3,4] low-level circulating cardiac troponins have emerged as markers of subclinical myocardial injury and adverse prognosis in stable CVD and in population-based cohorts. Previous studies have consistently shown that hs-cTnI and hs-cTnT (high-sensitivity cardiac troponin T) are associated with incident cardiovascular events and mortality and may improve risk prediction beyond conventional risk factors.[5–9] However, most available evidence is based on single baseline troponin measurements and long-term event prediction. Whether reversible changes in hs-cTnI within the analytical reference range mirror short-term modifications in cardiovascular risk profiles during primary prevention remains less well established.

Within the CV-PREVITAL framework, this exploratory substudy therefore aimed to determine whether detectable hs-cTnI concentrations, defined according to the assay lower limit of detection, were associated with cardiovascular risk scores derived from widely used algorithms, and whether changes in hs-cTnI over 12 months paralleled changes in clinical, laboratory, lifestyle, and risk-score profiles.

METHODS

Cohort Description

This single-center ancillary study was nested within CV-PREVITAL, a large multicenter project; its rationale and design have been described elsewhere.[2]

In brief, 27 560 individuals from the general population, aged ≥45 years and in primary cardiovascular prevention, were enrolled through the Italian Cardiology Network and affiliated local health services. Exclusion criteria were age <45 years and a history of overt CVD. At baseline, all participants underwent a comprehensive clinical assessment and received counseling on lifestyle measures to maintain or improve cardiovascular health. A second visit at 12 months was scheduled to assess changes in cardiovascular risk scores and major risk factors.[2]

From July 2022 to March 2024, a subgroup of 810 subjects (288 men and 522 women) was recruited for the troponin substudy at the Department of Cardiology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituti Clinici Scientifici Maugeri, Montescano and Pavia, Italy. The troponin substudy included consecutive eligible participants attending the enrolling center during the recruitment window and was driven by logistical availability of sampling and laboratory capacity. The sex distribution reflects center attendance as the study was not designed to be sex-balanced. The study protocol was approved by the Istituti Clinici Scientifici Maugeri Ethics Committee (CE 2575), and all participants provided written informed consent.

At follow-up, after 12 months, all examinations and questionnaires were repeated, and adverse events were recorded. Due to feasibility constraints, hs-cTnI was assessed in 473 subjects (58.4% of the cohort) who had a complete set of available data both at baseline and follow-up.

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ascertainment of Baseline Characteristics

Information on medication use and past medical history was collected via online questionnaires and verified

by a cardiologist during the baseline visit. This visit also included a physical examination and measurements of arterial pressure, heart rate, body mass index (BMI), and waist circumference. Lifestyle habits, including physical activity, diet, smoking and alcohol consumption, and sleep quality, were self-reported via online questionnaires. Cardiovascular risk was estimated using the following validated algorithms: the Progetto Cuore score, which estimates the 10-year probability of a first major cardiovascular event (heart attack or stroke) in individuals aged 35 to 69 years[10]; the Framingham Risk Score, which estimates the 10-year risk of heart attack in individuals without diabetes aged 30 to 79 years with no prior history of coronary heart or vascular disease[11]; the atherosclerotic CVD score, which estimates the 10-year probability of a first major cardiovascular event (heart attack or stroke), including race as a risk factor, in individuals aged 40 to 79 years[12]; the Finnish Diabetes Risk Score (FINDRISC), which defines the risk of an individual without diabetes developing type 2 diabetes within 10 years[13]; the Moli-sani risk score, which measures the combined impact of modifiable cardiovascular risk factors have on cardiovascular risk.[14] In addition, adherence to the Mediterranean diet was assessed using the Prevention With Mediterranean Diet (Predimed) score[15] and sleep quality with the Pittsburgh Sleep Quality Index.[16]

Laboratory Measurements

Venous blood samples were obtained after an overnight fast at the baseline and follow-up visits. Standard biochemical parameters (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and glycated hemoglobin) were measured using routine clinical assays (additional information is available in Data S1). Hs-cTnI concentrations were determined using a commercially available immunoassay (ARCHITECT i-STAT, Abbott Diagnostics). According to the manufacturer, the assay's lower detection limit is 1.3 ng/L, with reference ranges of undetectable – 15.6 ng/L for women and undetectable – 34.2 ng/L for men.

For the present analyses, participants were classified as having undetectable or detectable hs-cTnI according to the assay lower limit of detection, namely 1.3 ng/L. Values below this threshold were not imputed as numerical concentrations but analyzed as undetectable.

A pilot analytical study was performed to assess the reproducibility of hs-cTnI measures in the blood obtained from an independent cohort of 52 healthy subjects. The details and results of the pilot study are reported in the STROBE Checklist.

Statistical Analysis

The distribution of continuous variables was assessed by visual inspection of histograms and Q–Q plots. Given the relatively large sample size, formal tests of normality were not used as a primary criterion for selecting statistical tests. Continuous variables are reported as mean ± SD, and categorical variables as absolute and relative frequencies (%).

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Changes in paired dichotomous variables between baseline and follow-up were assessed using McNemar's test; the exact version of the test was used when appropriate.

Between-group comparisons of continuous variables were performed using the Student's *t* test for independent samples. When the assumption of homogeneity of variances, assessed using the Brown–Forsythe test, was violated, Welch's *t* test (Satterthwaite approximation) was applied. Effect sizes for between-group comparisons were expressed as Cohen's d for continuous variables and as odds ratios (OR) with 95% CIs for dichotomous variables.

Within-group comparisons for paired data (baseline and follow-up measurements) were performed using linear mixed-effects models with a random intercept for subjects to account for within-subject correlation. The fixed effect of time was used to estimate mean changes over time. Longitudinal effect sizes were reported as standardized mean differences, calculated as the ratio between the estimated least-squares mean difference (follow-up minus baseline) from the mixed-effects model and the model-based within-subject residual SD.

To assess within-person changes in hs-cTnI, subjects were primarily categorized according to the change in troponin between baseline and 12 months as decreased versus not decreased, where a decrease was defined as either a reduction in troponin from baseline to follow-up or a transition from detectable at baseline to nondetectable at follow-up. In addition, participants were categorized according to the percentage change between baseline and follow-up as decreased, stable, or increased. Sensitivity analyses were performed using alternative pragmatic cutoffs of 20% and 30% for relative change in troponin, chosen to reflect small-to-moderate clinically relevant within-person variation and to assess robustness across definitions of meaningful change. This pragmatic approach was informed by the concept of reference change values, which account for analytical and biological variability and are used to interpret meaningful changes in serial biomarker measurements.[17]

Longitudinal changes in cardiovascular risk scores were analyzed using generalized linear mixed models, including time, troponin change category, and their interaction as fixed effects, and participant-specific random intercepts to account for repeated measures.

Effect sizes for longitudinal group differences were expressed as ratios of change over time (interaction

Table 1. Baseline Characteristics of the Study Population According to hs-cTnI Levels

	All (n=810)	hs-cTnI undetectable, <1.3 ng/L (n=488)	hs-cTnI detectable, ≥1.3 ng/L (n=322)	*P* value	Effect size
Age, y	56.2±6.9	54.8±6.2	58.3±7.4	<0.0001*	0.527
Female sex, n (%)	522 (64.4)	373 (71.5)	149 (28.5)	<0.0001	0.261 (0.192–0.354)
Body mass index, kg/m^2	25.1±4.8	24.4±4.4	26.1±5.1	<0.0001*	0.352
Waist, cm	87.3±13.9	84.6±12.8	91.4±14.5	<0.0001*	0.503
Waist/height	0.52±0.08	0.51±0.07	0.54±0.08	<0.0001*	0.371
Systolic blood pressure, mm Hg	125.4±14.5	123.0±13.6	129.1±15.1	<0.0001*	0.424
Diastolic blood pressure, mm Hg	82.3±9.1	81.0±8.6	84.2±9.4	<0.0001	0.366
Heart rate, beats per min	72.1±10.6	73.4±10.4	70.1±10.6	<0.0001	−0.311
Total cholesterol, mg/dL	206±38	207±37	206±38	0.71	−0.027
Low-density lipoprotein cholesterol, mg/dL	130.3±39.1	130.3±42.7	130.3±32.9	0.99*	0.001
High-density lipoprotein cholesterol, mg/dL	58.2±13.9	59.3±13.6	56.4±14.1	0.003	−0.211
Triglycerides, mg/dL	95.6±54.7	93.9±53.4	98.4±56.5	0.25	0.082
Glycated hemoglobin, mmol/mol	38.9±5.9	38.5±5.9	39.6±5.8	0.010	0.186
Hypertension, n (%)	233 (28.8)	115 (23.8)	118 (36.7)	<0.0001	1.854 (1.361–2.525)
Type 2 diabetes, n (%)	24 (3.0)	15 (3.1)	9 (2.8)	0.83	0.913 (0.394–2.112)
Active smoking, n (%)	162 (20.0)	103 (21.1)	59 (18.3)	0.33	0.838 (0.587–1.197)
Family history of coronary artery disease, n (%)	219 (27.0)	135 (27.7)	84 (26.1)	0.70	0.931 (0.676–1.280)
Antihypertensive therapy, n (%)	225 (27.8)	116 (23.8)	109 (33.9)	0.002	1.661 (1.216–2.270)
Cholesterol-lowering therapy, n (%)	86 (10.6)	48 (9.8)	38 (11.8)	0.37	1.236 (0.787–1.941)
Hypoglycemic therapy, n (%)	18 (2.2)	11 (2.3)	7 (2.2)	0.94	0.970 (0.372–2.529)

Values are presented as mean±SD or n (%). *P* values are from unpaired *t* test (*: Welch's *t* test) or chi-square (categorical variables). Effect sizes are expressed as Cohen's d for continuous variables and as odds ratio (95% CI) for dichotomous variables. Subjects with hs-cTnI determination at baseline only n=337 (/810); Subjects with detectable troponin at baseline n=127 (/337); median (Q1, Q3) troponin at baseline: 2.3 (1.6, 3.9) ng/L. Subjects with hs-cTnI determination at both baseline and follow up n=473 (/810); Subjects with detectable troponin at baseline n=195 (/473); median (Q1, Q3) troponin: 2.2 (1.7, 3.4) ng/L. hs-cTnI indicates high-sensitivity cardiac troponin I.

ratio), derived from exponentiated group-by-time interaction terms from the mixed model, with corresponding 95% CIs. Between-group comparisons (3 groups) at each time point were performed using Tukey-adjusted least-squares mean contrasts.

Model assumptions were evaluated through inspection of conditional residuals and diagnostic plots.

Analyses were conducted using available data without imputation for missing data due to the fact that missingness was relatively low (<10% for most variables) and was considered unlikely to be systematically associated with participant characteristics or study outcomes.

All statistical tests were 2 tailed, and a *P* value <0.05 was considered statistically significant. Analyses were conducted using SAS/STAT, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Characteristics

A total of 810 participants were enrolled. Table 1 shows the baseline characteristics, including anthropometric measures, vital signs, cardiovascular risk factors, laboratory values, and medication use. The mean age was 56.2 years, and 64.4% of participants were female. hs-cTnI was measured at baseline and follow-up in 473 participants, who had a complete set of available data.

At baseline, hs-cTnI was undetectable (<1.3 ng/L) in 488 participants (59%) and detectable, within normal range, in 322 participants (41%). Detectable hs-cTnI levels were significantly associated with male sex (*P*<0.0001) and with postmenopausal status among women (32% versus 19%; *P*=0.012).

Compared with participants with undetectable hs-cTnI levels, those with detectable levels were older and had a higher BMI, larger waist circumference, and higher systolic and diastolic blood pressure (all *P*<0.0001). The effect size was in the range 0.366 to 0.527. Heart rate was lower in participants with detectable hs-cTnI (*P*<0.0001, effect size −0.311). The lipid profile was similar between the 2 groups, except for lower HDL cholesterol in the detectable group (*P*=0.003). glycated hemoglobin was higher in the detectable group (*P*=0.010). The prevalence of active smoking and type 2 diabetes did not differ. The use

Table 2. Baseline Cardiovascular Risk Scores, Diet Adherence, and Sleep Quality According to hs-cTnI Levels (n=810)

	All (n=810)	hs-cTnI undetectable, <1.3 ng/L (n=488)	hs-cTnI detectable, ≥1.3 ng/L (n=322)	*P* value	Effect size
Progetto Cuore risk score	3.77±4.14	2.82±3.08	5.31±5.07	<0.0001*	0.630
Framingham risk score	10.59±8.90	8.56±7.20	13.71±10.28	<0.0001*	0.602
Atherosclerotic cardiovascular disease risk score	6.09±6.44	4.50±5.00	8.55±7.55	<0.0001*	0.661
Finnish Diabetes Risk Score	12.20±4.91	11.53±4.92	13.20±4.72	<0.0001	0.344
Moli-sani risk score	2.41±1.94	2.32±1.89	2.54±2.00	0.11	0.114
Prevention With Mediterranean Diet score	6.99±1.85	6.90±1.85	7.14±1.84	0.08	0.132
Pittsburgh Sleep Quality Index score	6.11±3.29	6.23±3.26	5.94±3.33	0.23	−0.085

Values are presented as mean±SD. *P* values are from unpaired *t* test (*: Welch's *t* test). Effect sizes are expressed as Cohen's d. hs-cTnI indicates high-sensitivity cardiac troponin I.

of antihypertensive therapy was more prevalent in the detectable group (*P*=0.002, effect size 1.661).

All major cardiovascular risk scores were higher in participants with detectable, within normal range, hs-cTnI than in those with undetectable levels, except for the Moli-sani risk score (Table 2). No differences were observed between the groups in terms of the Predimed and Pittsburgh Sleep Quality Index scores.

Follow-Up

At 1 year, the proportion of participants with undetectable hs-cTnI had increased from 59% to 79% (*P*<0.0001). The proportion of participants with detectable, within normal range, hs-cTnI decreased from 41% to 21% (*P*<0.0001) (Figure). Only 6.1% of participants shifted from undetectable to detectable levels, while 58.5% shifted from detectable to undetectable levels. Reductions were more pronounced in men (51%) than in women (26.5%; *P*<0.0001). At follow-up, Progetto Cuore, Framingham Risk Score, atherosclerotic CVD score, and Moli-sani score decreased significantly, whereas FINDRISC increased slightly but significantly (Table 3). The effect size was −0.600 for the Moli-sani score but was smaller for other risk scores. The Predimed score improved while the Pittsburgh Sleep Quality Index remained unchanged. Despite the reduction in the number of subjects with detectable hs-cTnI, those in this group still had higher risk scores than those with undetectable levels (Table 4).

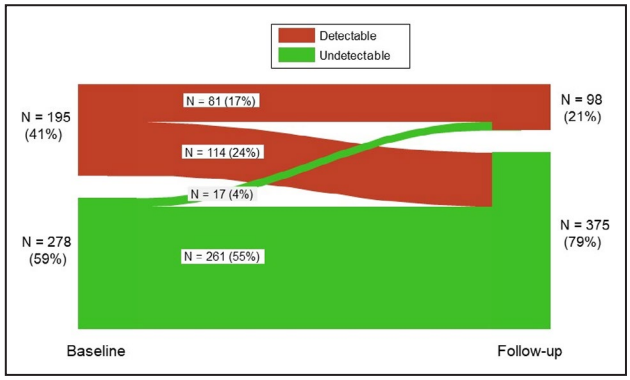

Figure. Sankey diagram of hs-cTnI values at baseline and 12-month follow-up (n=473).
The figure illustrates the number and proportion of participants shifting from undetectable to detectable hs-cTnI levels and vice versa. Additional analyses stratified by therapy stability vs therapy modification are provided in Table 6. hs-cTnI indicates high-sensitivity cardiac troponin I.

Overall, there were improvements in clinical parameters, with significant reductions in waist circumference, blood pressure, heart rate, and total and low-density lipoprotein cholesterol (Table S1). However, BMI, high-density lipoprotein cholesterol, and triglycerides remained unchanged, while glycated hemoglobin increased significantly (*P*<0.001).

There was also a significant change in medication use: the use of antihypertensives, lipid-lowering drugs, and hypoglycemics all increased (Table 5). Troponin transition stages, categorized by therapy stability or modification, are summarized in Table 6 and Figure S1. They show that there were no significant differences in the proportion of participants in the various stages of transition, including the transition from detectable to undetectable hs-cTnI.

When participants were stratified according to their individual changes in hs-cTnI between baseline and 12 months (decreased, stable or increased), as defined by percentage change thresholds of 20% and 30%, no significant differences were observed in changes to any cardiovascular risk score across the troponin-change categories (see Tables S2 and S3).

When changes in cardiovascular risk scores from baseline to 12 months were analyzed according to decreased versus not decreased hs-cTnI, no significant between-group differences were observed for Progetto Cuore, Framingham Risk Score, atherosclerotic CVD score, FINDRISC, Moli-sani score, or Pittsburgh Sleep Quality Index. A significant between-group difference was observed only for the Predimed score (*P*=0.0065,

Table 3. Cardiovascular Risk Scores, Diet Adherence, and Sleep Quality at Baseline and 12-Month Follow-Up in a Subset of Participants (n=473)

	Baseline	Follow-up	*P* value for time effect	Effect size
Progetto Cuore risk score	3.48±3.66	3.22±3.49	0.0007	−0.229
Framingham risk score	10.21±8.55	8.86±7.43	<0.0001	−0.421
Atherosclerotic cardiovascular disease risk score	5.19±5.19	4.74±4.98	<0.0001	−0.320
Finnish Diabetes Risk Score	11.93±4.78	12.36±4.64	0.0006	0.223
Moli-sani risk score	2.50±1.91	1.88±1.77	<0.0001	−0.600
Prevention With Mediterranean Diet score	6.94±1.84	7.21±1.90	0.004	0.198
Pittsburgh Sleep Quality Index score	6.45±3.29	6.47±3.32	0.86	0.011

Values are presented as mean±SD. *P* values refer to the fixed effect of time estimated using linear mixed-effects models for repeated measures. Effect sizes are expressed as standardized mean differences.

effect size 1.072) (Table 7). Exploratory analyses examining a potential dose–response relationship between the magnitude of change in hs-cTnI and changes in cardiovascular risk scores did not identify consistent or clinically meaningful associations (data not shown).

DISCUSSION

The key finding of our study is that, 1 year after a single cardiovascular counseling session aimed at promoting a healthier lifestyle in a general population we observed an improvement in the cardiovascular health of the population as shown by a reduction of both hs-cTnI levels and cardiovascular risk scores. The fact that hs-cTnI levels are reduced after 1 year supports the importance of early implementation of preventive measures against heart disease. Conversely, an increase in hs-cTnI levels in some seemingly healthy individuals may indicate the need for a closer clinical monitoring.

In our population of middle-aged individuals undergoing primary cardiovascular prevention, hs-cTnI concentrations were undetectable in 59% of individuals and within the normal range in the remaining 41%. This high prevalence of undetectable hs-cTnI is probably due to the relatively young age of the population (56.2±6.9 years). Indeed, circulating troponin

Table 4. Cardiovascular Risk Scores, Diet Adherence, and Sleep Quality at Baseline and 12-Month Follow-Up According to hs-cTnI Levels in a Subset of Participants (n=473)

	Baseline				Follow-up			
	hs-cTnI undetectable, <1.3 ng/L (n=278)	hs-cTnI detectable, 3.08±2.42 ng/L (n=195)	*P*-value	Effect size	hs-cTnI undetectable, <1.3 ng/L (n=375)	hs-cTnI detectable, 3.83±3.52 ng/L (n=98)	*P* value	Effect size
Progetto Cuore risk score	2.58±2.65	5.17±5.07	<0.0001*	0.682	2.81±3.06	4.91±4.49	<0.0001 *	0.620
Framingham risk score	8.01±6.11	13.33±10.38	<0.0001*	0.654	8.01±6.63	12.15±9.27	<0.0001 *	0.570
Atherosclerotic cardiovascular disease risk score	3.76±3.73	7.69±6.77	<0.0001*	0.763	4.20±4.67	7.21±6.00	<0.0001 *	0.606
Finnish Diabetes Risk Score	11.16±4.72	12.99±4.68	<0.0001	0.390	12.28±4.50	12.64±5.16	0.49	0.078
Moli-sani risk score	2.46±1.86	2.58±1.98	0.48	0.066	1.85±1.74	1.99±1.87	0.50	0.077
Prevention With Mediterranean Diet score	6.78±1.87	7.27±1.79	0.005	0.265	7.21±1.91	7.18±1.91	0.90	−0.016
Pittsburgh Sleep Quality Index score	6.72±3.31	6.07±3.22	0.036	−0.197	6.52±3.34	6.28±3.23	0.52	−0.074

Values are presented as mean±SD. *P* values are from unpaired *t* test (*: Welch's *t* test). Effect sizes are expressed as Cohen's d. hs-cTnI indicates high-sensitivity cardiac troponin I.

Table 5. Pharmacological Therapy at Baseline and 12-Month Follow-Up (n=473)

	Baseline		Follow-up	
	Subjects, n (%)	Drugs, n	Subjects, n (%)	Drugs, n
Antihypertensive therapy	129 (27.3)	1–5	160 (33.8)*	1–4
Cholesterol-lowering therapy	56 (11.8)	1–2	87 (18.4)*	1–2
Hypoglycemic therapy	6 (1.3)	1–3	15 (3.2)†	1–3

Values are presented as n (%).
*P<0.0001 (Exact McNemar's test).
†P=0.004 (Exact McNemar's test).

concentrations are known to increase with age in healthy individuals.[18,19] Furthermore, our participants were in good overall health and demonstrated a high level of awareness of, and attention to, their lifestyle. Nevertheless, we observed less favorable clinical parameters in those with detectable hs-cTnI, including higher BMI, waist circumference and arterial blood pressure, as well as lower high-density lipoprotein cholesterol and higher glycated hemoglobin levels, suggesting that subclinical cardiac injury may already be present (Table 1). The only counterintuitive finding was that participants with detectable hs-cTnI had a lower heart rate than those with undetectable levels. This seemingly paradoxical result can most likely be explained by the higher proportion of women in the undetectable group. This is consistent with previous studies of healthy middle-aged individuals showing that the mean heart rate tends to be lower in men than in age-matched women.[20]

Interestingly, blood hs-cTnI levels varied according to cardiovascular risk scores calculated using established algorithms, including the Progetto Cuore, Framingham, atherosclerotic CVD, and Moli-sani models. Specifically, we found that subjects with undetectable hs-cTnI consistently had lower risk scores, whereas those with detectable hs-cTnI had higher scores (Table 2).

One year after the cardiovascular counseling visit, which included advice on lifestyle modifications as well as optimizing pharmacological therapy, we still observed differences in risk scores between participants with detectable and undetectable troponin concentrations (Table 4), despite the entire cohort showing a modest but significant reduction in overall cardiovascular risk (Table 3). These findings suggest a possible relationship between blood troponin levels and cardiovascular health status. We propose that even within the normal range, circulating hs-cTnI levels may reflect a minimal degree of cardiac injury, and we speculate that hs-cTnI may serve as a dynamic marker when testing preventive interventions or monitoring disease progression.

At the 12-month follow-up, 79% of subjects had undetectable hs-cTnI levels, compared with 59% at baseline, suggesting an overall improvement in cardiovascular health (). Although there was an improvement in clinical parameters across the population as a whole, no significant differences were observed between participants with detectable versus undetectable hs-cTnI levels, except for heart rate (Tables S1). This is likely due to the small proportion of the detectable hs-cTnI group at follow-up (about one fifth of the total). The observed decrease in heart rate in the detectable group could be related to the higher proportion of men (33%) than women (19%) who shifted from detectable to undetectable hs-cTnI levels during the follow-up period.

Although risk scores differed significantly at each time point when subjects were categorized according to troponin detectability (Table 4), indicating a higher level of risk for subjects with detectable troponin, the difference in risk scores was less evident when analyzing changes in cardiovascular risk scores according to troponin individual trajectories (increase, decrease,

Table 6. Hs-cTnI Transitions From Baseline to 12-Month Follow up Stratified by Therapy Stability Versus Modification

	Therapy stable, n (%)	Therapy changed, n (%)
hs-cTnI baseline <1.3 ng/L hs-cTnI follow up <1.3 ng/L	234 (55.9)	27 (49.2)
hs-cTnI baseline ≥1.3 ng/L hs-cTnI follow up <1.3 ng/L	101 (24.2)	13 (23.6)
hs-cTnI baseline <1.3 ng/L hs-cTnI follow up ≥1.3 ng/L	14 (3.3)	3 (5.4)
hs-cTnI baseline ≥1.3 ng/L hs-cTnI follow up ≥1.3 ng/L	69 (16.6)	12 (21.8)
Total	418	55

Results are expressed as number of subjects (n) and percentage (%) in each category. P=0.83 (Fisher exact test). hs-cTnI indicates high-sensitivity cardiac troponin I.

Table 7. Twelve-Month Change in Cardiovascular Risk Scores According to Decreased Versus Not Decreased hs-cTnI (n=473)

	hs-cTnI decreased n=165		hs-cTnI not decreased n=308		*P* values			
	Baseline	Follow-up	Baseline	Follow-up	*P*-value for group effect	*P*-value for time effect	*P*-value for group×time effect	Effect size
Progetto Cuore risk score	4.94±4.58	4.55±4.30	2.75±2.85	2.56±2.80	<0.0001	<0.0001	0.9231	1.003 (0.939–1.071)
Framingham risk score	13.53±10.65	11.76±9.04	8.44±6.53	7.31±5.87	<0.0001	<0.0001	0.6892	0.985 (0.917–1.059)
Atherosclerotic cardiovascular disease risk score	7.57±6.34	7.02±6.33	3.98±3.99	3.58±3.63	<0.0001	<0.0001	0.6674	0.986 (0.924–1.052)
Finnish Diabetes Risk Score	13.08±4.55	13.47±4.06	11.32±4.79	11.76±4.83	<0.0001	0.0005	0.9119	0.997 (0.945–1.051)
Moli-sani risk score	2.55±1.92	2.00±1.71	2.48±1.90	1.81±1.80	0.8480	<0.0001	0.6642	1.028 (0.907–1.165)
Prevention With Mediterranean Diet score	7.28±1.81	7.24±1.92	6.74±1.83	7.19±1.90	0.1005	0.0484	0.0065	1.072 (1.020–1.128)
Pittsburgh Sleep Quality Index score	6.03±3.24	6.21±3.29	6.68±3.29	6.61±3.33	0.0370	0.4996	0.3397	0.959 (0.881–1.045)

Values are presented as mean±SD. *P* values for main effects of group and time and group×time interaction are reported. Effect sizes for longitudinal group differences are expressed as ratio of change over time between groups (interaction ratio) with corresponding 95% CIs. hs-cTnI indicates high-sensitivity cardiac troponin I.

or stability) (see Tables S2 and S3). Similarly, when the 12-month change in each risk score was quantified in participants with decreased versus not decreased hs-cTnI (see Table 7), no clinically meaningful differences were observed, but a trend toward more pronounced changes in risk scores was noted in subjects with a decrease in troponin. Based on these observations, we speculate that troponin dynamics may capture information not fully reflected by changes in conventional risk scores over the same time frame.

The observed 12-month reduction in risk scores are likely attributable to lifestyle changes, including dietary habits (Table 3). Indeed, the Predimed score, an index of adherence to the Mediterranean diet, significantly improved at follow-up. Similarly, the Moli-sani risk score, which incorporates dietary habits into cardiovascular risk assessment, was reduced. As a number of subjects had new prescriptions or an increase in previous therapy, it is possible that optimizing pharmacological therapy contributed to the observed benefits (Table 5). To investigate whether changes in troponin levels were driven by changes in therapy, we examined troponin transitions categorized by changes in pharmacological therapy between the baseline and follow-up stages (Table 6). However, we observed no differences in the transition from detectable to undetectable hs-cTnI between participants with stable or changed therapy. The lack of data on adherence to therapy prevented us from assessing the effectiveness of therapy.

Several previous studies have assessed the prognostic value of cardiac troponins in apparently healthy populations.[21–23] More recently, McEvoy et al. investigated the predictive role of cardiac troponins in 9810 subjects without cardiovascular disease from the US National Health and Nutrition Examination Survey, followed for a median of 17.2 years. They demonstrated that both hs-TnT and hs-cTnI assays provide distinct prognostic information on mortality in the general population.[24] Furthermore, 2 meta-analyses concluded that circulating cardiac troponins in the general population have strong prognostic value, being independently associated with cardiovascular risk and mortality.[25,26] A recent meta-analysis[27] suggested that hs-cTnI may help to refine risk stratification in apparently healthy individuals beyond traditional scores and that monitoring hs-cTnI over time could identify those who would benefit most from lifestyle or pharmacological interventions. Interestingly, a recent study showed that modifiable lifestyle risk factors are associated with elevated concentrations of hs-cTnI and hs-TnT in a cohort of patients undergoing coronary angiography with no evidence of clinical signs of myocardial infarction.[28] Our results, in a healthy population, align with these findings.

In our study, it was not yet possible to assess cardiovascular events because of the short observation period; however, this evaluation will be conducted in due course according to the CV-PREVITAL protocol,

which includes a 7-year follow-up for the collection of major cardiovascular outcomes.

Strengths and Limitations

Strengths

This study was conducted within the framework of the large, multicenter CV-PREVITAL project, ensuring high methodological quality and standardized data collection. Hs-cTnI measurements were performed with a validated high-sensitivity assay and repeated at 2 time points, allowing the evaluation of dynamic changes over time in the same subjects. Cardiovascular risk was assessed using multiple validated algorithms, providing robust cross-validation of the findings. Finally, the study population consisted of apparently healthy, middle-aged individuals from the general population, enhancing the relevance of the results for primary prevention strategies.

Limitations

This exploratory study also has some limitations, including a single-center ancillary study, which may affect generalizability; possible confounding from unmeasured variables such as medication adherence and socioeconomic factors; and short follow-up (12 months), without adjudicated cardiovascular events (7-year follow-up ongoing). Given the observational design and use of risk scores rather than hard outcomes, hs-cTnI should be considered a candidate monitoring marker pending prospective validation on events. In interpreting detectable versus undetectable hs-cTnI, we acknowledge that the limit of detection is an analytical property of the assay rather than a biological threshold, and limit of detection-based categorization is not bioequivalent across troponin assays. New technologies will likely reduce the limit of detection for hs-cTnI—currently equal to 1.3 ng/L in this assay—enabling the quantification of circulating hs-cTnI levels in most of the middle-aged healthy population in the future. In addition, although current clinical assays are formulated to detect all circulating forms of troponins, a recent work has shown that cardiac troponins undergo significant fragmentation in the bloodstream.[29] Future assays able to detect specific troponin fragments may be useful for cardiovascular risk assessment.

We also acknowledge important sex differences in the distribution of hs-cTnI in healthy individuals; a sex-agnostic limit of detection could fail to identify higher-risk women. Moreover, hs-cTnI may be influenced by noncoronary conditions such as renal impairment and structural heart disease, which we consider as potential confounders and limitations where relevant. In our population, besides coronary disease and structural heart disease, which were exclusion criteria, there were no patients who reported a history of chronic kidney failure.

Finally, participants without hs-cTnI assessment at 12 months differed slightly from those with paired measurements, being on average older and showing a slightly less favorable cardiometabolic risk profile, including higher Hb-A1c levels, greater use of glucose-lowering therapy, and higher estimated cardiovascular risk. These differences are consistent with nonrandom loss to follow-up and may reflect differential involvement in study procedures, logistical barriers to repeat visits, or greater clinical complexity.

Although attrition bias related to differential follow-up is acknowledged as a limitation and cannot be completely ruled out, the consistency of the main findings across complementary descriptive and exploratory analyses supports the overall robustness of the observed associations.

CONCLUSIONS

In a general population undergoing primary prevention, detectable hs-cTnI, even within the normal range, identified participants with a less favorable cardiovascular risk profile. Over 1 year, hs-cTnI detectability and several cardiovascular risk scores improved; however, longitudinal hs-cTnI changes were not consistently associated with changes in risk scores. These findings support hs-cTnI as a candidate monitoring biomarker in primary prevention, but its clinical utility requires prospective validation against adjudicated cardiovascular outcomes.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figure S1

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