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ORIGINAL

Cardiovascular risk stratification in asymptomatic individuals in Bitola, North Macedonia by using High sensitive Troponin I Assay

Estratificación del riesgo cardiovascular en individuos asintomáticos de Bitola, Macedonia del Norte, mediante el uso de la prueba de troponina I de alta sensibilidad

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Abstract

Objectives: The aim of our prospective cohort study in Macedonia was to evaluate the distribution of hs-cTnI concentrations in health individuals to stratified cardiovascular risk.
Background: The latest generations of hs-cTnI could be used for the stratification of cardiovascular risk in the general population, using values within the normal range.
Methods: Study was performed from one year period in 2021 year. We measured hs-cTnI concentrations in 1201 participants 690 males and 511 females by using Abbott Architect analyzer.
Results: We found that elevated risk for cardiovascular event is higher in males compared to females, also we confirm that risk of cardiovascular events increase significantly with age in both sexes, but is predominant in males.
Conclusion: The hs-cTnI assay provides detection of troponin in a significant proportion of asymptomatic individuals. Hs-cTnI allows us to act preventively in patients at increased risk by including statin therapy, weight regulation or lifestyle changes, intensifying physical activity, while its values are parallel to the modification of cardiovascular risk. Patients should be informed that there is a possibility of cardiovascular risk assessment and more massive hs-cTnI examination.

Key words: hs-cTnI, troponin, cardiovascular disease, risk stratification.

Resumen

Objetivos: El objetivo de nuestro estudio de cohorte prospectivo en Macedonia fue evaluar la distribución de las concentraciones de hs-cTnI en individuos sanos para estratificar el riesgo cardiovascular.
Antecedentes: Las últimas generaciones de hs-cTnI podrían utilizarse para la estratificación del riesgo cardiovascular en la población general, utilizando valores dentro del rango normal.
Métodos: El estudio se realizó durante un período de un año en 2021. Se midieron las concentraciones de hs-cTnI en 1201 participantes, 690 hombres y 511 mujeres, utilizando el analizador Abbott Architect.
Resultados: Encontramos que el riesgo elevado de eventos cardiovasculares es mayor en los hombres en comparación con las mujeres, también confirmamos que el riesgo de eventos cardiovasculares aumenta significativamente con la edad en ambos sexos, pero es predominante en los hombres.
Conclusión: El ensayo hs-cTnI proporciona la detección de troponina en una proporción significativa de individuos asintomáticos. La Hs-cTnI permite actuar de forma preventiva en los pacientes con riesgo aumentado incluyendo el tratamiento con estatinas, la regulación del peso o los cambios en el estilo de vida, intensificando la actividad física, mientras que sus valores son paralelos a la modificación del riesgo cardiovascular. Se debe informar a los pacientes que existe la posibilidad de evaluar el riesgo cardiovascular y realizar un examen más masivo de hs-cTnI.

Palabras clave: hs-cTnI, troponina, enfermedad cardiovascular, estratificación del riesgo.

Introduction

Cardiovascular disease remains the leading cause of mortality worldwide, accounting for one-third of deaths[1,2]. Cardiovascular risk stratification has long been based on risk factors: atherosclerosis, demographic characteristics such as gender and age, lifestyle, smoking and physical inactivity, history of co morbidities, such as diabetes mellitus, arterial hypertension and obesity, and circulating biochemical markers, such as increased total cholesterol and low-density lipoprotein cholesterol[3]. The most important risk factor in recent times have more recently been incorporated into practical risk prediction tools developed by scientific bodies, such as the SCORE by the European Society of Cardiology or the cardiovascular risk calculator by the American Heart Association[4,5].

Troponin is a cardiac-specific structural protein and guidelines recommend its use for the diagnosis and management of acute coronary syndrome[6]. Newly established technologies allow precise measurement of low circulating troponin concentrations in the general population[7]. Troponin concentration correlates with myocyte necrosis and apoptosis. They further correlate with the prevalence of cardiovascular risk factors, metabolic disorders, and cardiac hypertrophy or dysfunction[8,9]. Assessment of circulating troponin concentrations using a robust, highly sensitive assay might therefore be suitable to predict first and subsequent adverse events[10,11]. Introduction of cardiac troponin I and troponin T, into clinical practice improved dramatically the differential diagnosis of acute chest pain, providing a reliable means for the accurate diagnosis of acute coronary syndromes[12]. The impact of troponin is indicated by the fact that the universal definition of myocardial infarction recommends a troponin rise and fall as the first requirement for the diagnosis of any form of myocardial infarction. In addition to diagnosis, troponin aid significantly in the monitoring of patients with acute coronary syndromes and in the decision-making in the case of non-ST segment elevation acute coronary syndromes[13]. Furthermore, pathological troponin elevation is observed in many disease states and hs-cTnI are independent prognostic markers in several cardiovascular and non- cardiovascular conditions, such as acute coronary syndromes, chronic coronary artery disease, acute and chronic heart failure, cancer therapy-related cardiotoxicity and chronic kidney disease[14,15].

The use of troponin in addition to diagnostic purposes can also be used for prognostic information. Patients presenting with clinical evidence of ischemia and increased troponin have worse outcomes than those without detectable troponin in the circulation[16]. Even in patients with stable coronary artery disease, high-sensitivity assays have demonstrated that detectable concentrations of troponin portend a higher incidence of heart failure and cardiovascular death[17]. Troponin has also been proven to be a potent, independent indicator of recurrent ischemic events, and an estimate for the risk of death among patients presenting with acute coronary syndromes. The risk of death from cardiovascular disease correlates with troponin levels.

Predicting cardiovascular risk is important in the prevention and treatment of cardiovascular disease. Many risk estimation systems are in existence[18,19,20]. Different guidelines recommend different risk score calculators to assess the 10-year cardiovascular risk and their management depending on their risk scores[21,22].

The latest generations of hs-cTnI have enabled us to improve the diagnostic capacity of hs-cTnI, with its help we earlier and safer control and exclusion of acute coronary syndromes and non-acute coronary syndromes pathophysiology[13,23,24,25]. One of the key analytical requirements of hs-cTnI assay in order to be characterized as 'high-sensitivity' is its detectability in >_50% of apparently healthy individuals, as set by the International Federation of Clinical Chemistry and Laboratory Medicine[26]. With the help of this feature we can accurately calculate the 99th percentile, which is considered the upper limit of normal, and imposes a very low limit of detection of single-digit pg/mL, significantly lower than the 99th percentile[7]. The commercially available hs-cTnI assays provide high-detectability rates in symptomatic individuals, reaching 96% or higher in some cases[7,27]. This considerable detectability in asymptomatic individuals gave rise to the hypothesis that hs-cTnI could be used for the stratification of cardiovascular risk in the general population, using values within the normal range, that is between the lower limit of detection and the 99th percentile of normal.

The detection of a low threshold for troponin detection in asymptomatic patients has led to the hypothesis that hs-cTnI can be used to stratify cardiovascular risk in the general population by using values in the normal range, which is between the lower limit of detection and the 99th percentile of normal. The aim of our study was to evaluate the distribution of hs-cTnI concentrations between the sexes in a prospective cohort study in Macedonia, to investigate whether the association of hs-cTnI and risk of cardiovascular death differs between women and men, and to assess whether sex-dependent differences in cardiovascular risk are modified by hs-cTnI concentrations.

Materials and methods

We made a prospective cohort study in Macedonia in Bitola city in the period of January 2021 to January 2022. Our study was approved by the ethics committee and all study participants signed a written informed consent. We measured hs-cTnI concentrations in 1201

participants 690 males and 511 females. We prepared questionnaires about the health condition of the respondents, and they were filled in by the participants, we did a physical examination, and we took blood from specially trained nurses. Future more we collected clinical data on height, weight, and waist and hip circumference. We measured systolic and diastolic blood pressure with an automated device.

For hs-cTnI the 99th percentile values in a healthy reference population have been reported to be 16 pg/ml in women and 36 pg/mL in men[7]. Before analysis, samples were centrifuged at 3000 relative centrifugal force for 15 min. We measured hs-cTnI using Abbott Architect analyzer, with STAT High Sensitive Troponin assay. The limit of detection for the assay was 1.9 pg/ml (range 0-50 000 pg/ml). We divided total patients in 8 age groups i.e. younger than 20 years, 21-30, 31-40, 41- 50, 51-60, 61-70, 71-80,81-90 years.

Exclusion Criteria:

- Patient's with increased hs-cTnI values higher than16 pg/ml in women and 36 pg/ml in men
- Patient's with type 2 diabetes mellitus
- Primary and secondary renal diseases,
- Patient's having confounding factors like fever, pregnancy, women in menstrual period, congestive cardiac failure etc.
- Hypertensive patients with BP ≥ 160/100 mmHg

Table I: Gender-specific risk stratification cut-offs of future cardiovascular event.

Troponin level		
Risk	**Male (pg/mL)**	**Female (pg/mL)**
Low risk of future cardiovascular event	<6	<4
Moderate risk of future cardiovascular event	≥6 to ≤12	≥4 to ≤10
Elevated risk of future cardiovascular event	>12	>10

Table II: Risk stratification of future cardiovascular event.

Risk stratification of future cardiovascular event		
Risk	**Males participants and %**	**Females participants and %**
Low risk	440 participants (64%)	389 participants (76%)
Moderate risk	123 participants (18%)	91 participants (18%)
Elevated risk	127 participants (18%)	31 participants (6%)

Table III: Age and sex mean hsTnI values (n=1201).

Age in years	Males		Females	
	No. of cases n=690	Mean values of hsTnI	No. of cases n=511	Mean values of hsTnI
<20	12	1.64±1.54	5	1.2±1.6
20-30	29	1.46±1.23	10	1.4±2.5
31-40	72	2.66±4.3	43	0.69±1.48
41-50	101	3.93±5.06	70	1.55±2.36
51-60	120	5.23±6.21	115	2.05±2.38
61-70	203	7.47±7.65	126	3.28 ±3.8
71-80	114	9.19±7.08	107	4.5±3.92
81-90	39	12.37±6.93	35	6.4±4.2

Results

The recommended sex-specific hs-cTnI cut-offs for cardiovascular risk stratification in asymptomatic individuals are shown in **table I**. The following cut-off points we used to aid in stratifying the risk of cardiovascular disease in asymptomatic individuals[29-31].

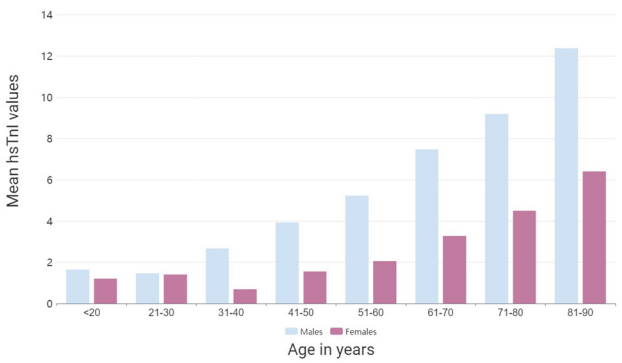
We measured circulating hs-cTnI concentrations in 690 (57%) men and 511 (43%) women. Mean age was 62±14,91 years for females, the age-range was 12-90 years, and mean age 57.93±16.07 years for males, and age-range was 7-90 years.

We evaluate the risk for cardiovascular event, and we found that elevated risk for cardiovascular event is higher in males compared to females. We found that 76% of females have low risk, 18% have moderate risk and 6% of females have elevated cardiovascular risk. Males with low risk were 64%, moderate risk have 18% and elevated risk for cardiovascular event have 18%.This dates are presented in **table II**.

Age and sex distribution of hsTnI values in all participants is mentioned in **table III**. We divided total patients in 8 age groups. Majority of patients belonged to 61-70 years in age group. We can notice that males in age group younger than 60 years have low risk for cardiovascular event; males in age groups 60 to 80 years have moderate risk for cardiovascular event and males older than 80 have elevated risk for cardiovascular event. About females, we can conclude that females younger than 70 years have low risk for cardiovascular event, and females older than 70 years have moderate risk for cardiovascular event.

In **figure 1** we present mean hsTn I value in different age groups in males and females.

Figure 1: Age and sex mean hsTnI values.



Discussion

The hs-cTnI assay provides detection of hs-cTnI in many asymptomatic individuals and can be used to overestimate the risk of cardiovascular events. Risk stratification in the asymptomatic population refers to the range of hs-cTnI values between the lower limit of detection and the 99th percentile of normal, but higher values are not included because they are indicators of disease. There are significant differences between men and women in terms of the prevalence of risk factors and the incidence of cardiovascular events. For instance, for a given age, blood pressure is higher in men than in women[32]; after puberty, left ventricular mass is greater in men than in women[33]; and women generally develop cardiovascular disease at an older age than men[34]. Age plays a vital role in the deterioration of cardiovascular functionality, resulting in an increased risk of cardiovascular disease in older adults[35,36]. The prevalence of cardiovascular disease has also been shown to increase with age, in both men and women, including the prevalence of atherosclerosis, stroke and, myocardial infarction[37].

The TIMI-IIIB study showed that in patients with acute coronary syndromes, mortality was higher in patients with elevated troponin I at the time of admission. Elevated troponin I level have an increased correlation with a relative risk of death of 7.8 among the group with the highest troponin levels, even after adjusting for age> 65, ST ECG depression, and other baseline variables. The GUSTO IIa study showed that elevated troponin T was significantly predictable for 30-day mortality in patients with acute myocardial ischemia, even after the assay was adjusted for electrocardiography category and CK-MB level[38].

The use of highly sensitive Troponin I allowed improved characterization of the cross-sectional distribution and correlations of cardiac troponin concentrations. The analysis of several studies confirmed that the circulating concentrations of cardiac troponins are significantly higher in men than in women[9,39-43]. The risk of cardiovascular events increases significantly with age in both sexes, but is predominant in males. In our study, we found that men under the age of 60 had a low risk of developing a cardiovascular; men aged 60 to 80 had a moderate risk of developing a cardiovascular, and men over the age of 80 had an increased risk of developing a cardiovascular disease. For females, we can conclude that females under 70 years of age have a low risk of cardiovascular event, and females older than 70 years have a moderate risk of cardiovascular event. According to the American Heart Association, heart disease and stroke in 2019 had an incidence of cardiovascular diseases of 77.2% in men and 78.2% in women aged 60-79 years, while the incidence of cardiovascular diseases was 89.3% in men and 91.8% in women, in adults over 80 years[44].

In the Nord-Trondelag health study of 9005 individuals without cardiovascular risk at baseline, the highest hs-cTnI tertiary (values> 10 ng/L in women and >12 ng/L in men) was associated with a 3.6-fold higher risk adjustment from cardiovascular death or hospitalization for myocardial infarct at median follow-up of 13.9 years compared with the lowest tertiary[31]. In another analysis of the same study, the predictive value of hs-cTnI for cardiovascular mortality was higher in women than in men (area below 0.84 versus 0.72)1[0]. This was confirmed by the ARIC study, which found that hs-TnI was more strongly associated with incidental coronary heart disease in women than in men[45]. These studies are very important because women are less involved in primary cardiovascular prevention and other cardiovascular examinations[46,47].

A comprehensive meta-analysis of 154,052 asymptomatic individuals showed that an increase in hs-cTnI and hs-cTnT within the reference values appropriate for both sexes, troponin levels were predictable for cardiovascular mortality and disease[48]; the highest third of hs-cTnI was associated with a 67% higher risk of fatal cardiovascular disease, a 59% higher risk of coronary artery disease, and a 35% higher risk of stroke compared to the lowest third. Some studies have shown that the prognostic value of hs-hs-cTnI is maintained in specific subgroups of the general population that are already at increased risk according to established risk factors, allowing further stratification of cardiovascular risk beyond these prognostic factors.

Conclusions and perspectives

The hs-cTnI assay provides detection of troponin in a significant proportion of asymptomatic individuals, enabling it to be considered for stratification of cardiovascular risk in the general population based on a single measurement. Hs-cTnI allows us to act preventively in patients at increased risk by including statin therapy, weight regulation or lifestyle changes, intensifying physical activity, while its values are parallel to the modification of cardiovascular risk. Patients should be informed that there is a possibility of cardiovascular risk assessment and more massive hs-cTnI examination. A guide to how to influence the lifestyle of patients at risk can be developed.

Conflict of Interest

The authors declare that no competing interests exist.

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