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Plasma homocysteine and the severity of heart failure in patients with previous myocardial infarction

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Abstract

Background: *Homocysteine is considered to be a risk factor, or an indicator of risk, for the development of cardiovascular disease. Little data is available on its significance in patients with previous myocardial infarction. The aim of our study was to assess the plasma level of homocysteine and its relationship with the severity of heart failure in patients with chronic myocardial infarction.*

Methods: *We studied 144 patients with previous myocardial infarction. Patients were divided into two groups according to the presence or absence of heart failure, as certified by clinical evidence of heart failure and by echocardiographic criteria for left ventricular systolic dysfunction.*

Results: *Of the patients with prior myocardial infarction (144; 63.6 ± 9.6 years) included in the study, 65 had heart failure. The mean level of homocysteine was significantly higher in the heart failure group (18.9 μmol/L) than in the non-heart failure group (14.1 μmol/L; $p \leq 0.001$). Our study demonstrated that there is a statistically significant correlation between homocysteine plasma levels and the severity of heart failure in patients with prior myocardial infarction. Homocysteine levels have proved to become higher with NYHA class progression. A significant cross-sectional correlation has been assessed between homocysteine and tissue Doppler echocardiography parameters.*

Conclusions: *Increased plasma homocysteine levels independently correlate with the severity of heart failure in patients with chronic myocardial infarction. We suggest that homocysteine can be used in clinical practice as a valuable heart failure risk marker in patients with chronic myocardial infarction.* (Cardiol J 2011; 18, 1: 55–62)

Key words: homocysteine, myocardial infarction, left ventricular dysfunction, heart failure

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Introduction

Myocardial infarction (MI) is an important factor in the occurrence of heart failure (HF) [1]. Its association with other risk factors, such as left ventricular hypertrophy (LVH), valvular heart disease, hypertension, diabetes mellitus, cigarette smoking, obesity, and dyslipidemia [2], doubles or trebles the risk of HF development [3].

Recently, the elevation of plasma homocysteine (Hcy) level has been recognised as a risk factor for HF [4, 5]. In experimental models, hyperhomocysteinemia has been shown to induce LVH and cardiac fibrosis which determine systolic and diastolic dysfunction, as well as increase brain natriuretic peptide (BNP) expression [6].

Theoretically, elevated Hcy levels could promote HF by several mechanisms: stimulation of collagen production by vascular smooth muscle cells and inhibition of endothelial cell growth; promotion of oxidative stress; stimulation of matrix metalloproteinase production which promotes endothelial dysfunction; or reduction of vasodilator capacity, ultimately leading to atherosclerosis [7].

In humans, a moderately increased plasma level of Hcy and genetic factors associated with enzymatic abnormalities of folic acid and Hcy metabolism play a major role in the development of coronary heart disease (CHD) and hence of HF [8].

The normal concentration of plasma Hcy ranges between 5 and 15 μmol/L; elevations of plasma Hcy from 15 to 30 μmol/L, 30 to 100 μmol/L and $>$ 100 μmol/L are classified as mild/moderate, intermediate and severe hyperhomocysteinemia, respectively [9].

Prospective data in high-risk patients has suggested that mild or moderate hyperhomocysteinemia [10] could be a risk factor for recurrent cardiovascular events and overall mortality [11].

Patients with previous MI are at risk of developing HF. Although the incidence of HF after MI has diminished in recent decades, it remains a common complication which occurs in up to 45% of cases. Moreover, up to 60% of MI will result in LV systolic dysfunction, depending on the exact definition used [12].

Our study aims to determine whether the presence of HF is associated with elevated levels of Hcy $>$ 15 μmol/L and to determine the relationship between Hcy and the severity of HF in patients with prior MI.

Methods

Patients

We studied 144 consecutive patients with previous MI. This study was conducted according to the Helsinki Declaration on Studies on Humans and approved by the local ethics committee.

Only patients with a history of MI within the last three months, as defined by international criteria, were included in our study.

The main exclusion criteria were: major events during hospitalization (i.e. neoplasia, inflammatory diseases, infections, hypotension, shock, and renal impairment); ongoing clinical instability (such as angina or arrhythmia); surgical interventions in the last two months or subsequent dyslipidemia as a result of hypothyroidism, nephrotic syndrome or cholestasis.

Patients were divided into two groups according to their LV systolic function and clinical evidence of HF according to the New York Heart Association (NYHA) classification criteria: Group 1 (the study group) included patients with reduced LV ejection fraction (LVEF) $\leq$ 40% and clinical evidence of HF; Group 2 (the control group) consisted of patients with LVEF $>$ 40% in which no clinical evidence of HF had been identified.

Echocardiography variables

All patients were studied by conventional and tissue Doppler echocardiography using a Hewlett-Packard Sonos 5500, Philips, ultrasound system, using a 2.5 MHz wide-angle phased-array transducer. Recordings were made via simultaneous superimposed electrocardiography.

Conventional echocardiography 2D-, M-mode and Doppler was used for each patient. Tracings from the parasternal long axis view were used to measure septal thickness, LV diameter at end-diastole and end-systole, and posterior wall thickness. LVEF was derived from Simpson's modified single plane method using the apical four-chamber view [13]. We considered LVEF $<$ 40% to be an accurate marker for LV systolic dysfunction.

Comprehensive assessment of LV diastolic function included transmitral pulsed wave Doppler from an apical four-chamber view. From the transmitral flow, the peak early (E) and late atrial (A) diastolic velocities, E-deceleration time (DT) and isovolumetric relaxation time were successfully recorded for all patients. Normal diastolic function

was defined as an E/A ratio of 1–1.5 and a DT of 160–230 ms. The classification of diastolic dysfunction according to echocardiographic criteria included the following categories: 1) abnormal relaxation pattern; 2) pseudonormal pattern; and 3) restrictive pattern. Impaired LV relaxation was defined as E/A < 1 and E-DT > 230 ms, while the pseudonormal pattern was defined as E/A of 1.5–2 and an E-DT < 230 ms. The restrictive pattern is defined by the combination of E/A > 2 and an E-DT < 160 ms.

Tissue Doppler echocardiography was used to assess LV longitudinal myocardial wall motion from the apical four-chamber view [14]. A sample volume of 2 mm was used, with the frame rate exceeding 100 m/s placed at the junction of the LV wall with the mitral annulus on the lateral myocardial segments. Peak systolic myocardial velocity during ejection (Sm), early (Em) and late (Am) diastolic velocities were measured by pulsed wave tissue Doppler imaging. The transducer was positioned to align the ultrasound beam with longitudinal LV motion. The ratio of E to lateral Em was used to estimate LV filling pressures. Normal diastolic function was defined as E/Em of < 8 and the impaired LV filling pressure was defined as E/Em of > 8 [14].

Blood sampling and biochemical testing

Venous blood samples were obtained after 12 hours of fasting; for measuring lipids, creatinine, Hcy and BNP, blood samples were drawn without stasis into evacuated glass tubes containing 1/100 volume of 0.5 mmol of ethylene diamine tetra acetic acid/L. Plasma was obtained by centrifugation at 1,500 g for 15 min and was measured in fresh samples.

The fasting Hcy levels were measured in all patients using fluorescence polarization immunoassay on Abbott Imx Analyzer [15]. In our study, normal Hcy levels range between 5 and 15 μmol/L, with elevations of 15 to 30 μmol/L, 30 to 100 μmol/L and > 100 μmol/L being classified as mild, moderate, and severe hyperhomocysteinemia, respectively. Plasma BNP was measured via commercial Triage assay (Biosite Diagnostics, Inc., San Diego, CA, USA) [16]. Plasma levels of total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG) were measured in all patients using enzymatic tests performed by a Roche-Hitachi 911 analyzer [17].

Other clinical variables

We recorded the presence of several risk factors, such as: age, sex, family history of CHD, smoking, hypertension, diabetes mellitus, obesity and dyslipidemia in accordance with international criteria. Family history of CHD was defined as a history of premature coronary artery disease in first-degree relatives (having occurred in those relatives at age < 55 for men and < 65 for women). Subjects who had smoked at least one cigarette per day over the previous two months were considered active smokers.

The presence of hypertension at baseline was defined as systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg or use of antihypertensive drugs, according to the current definition. The presence of diabetes at baseline was defined as fasting plasma glucose > 126 mg/dL (7 mmol/L) or use of oral hypoglycemic agents or insulin. A surrogate marker for obesity content is body mass index (BMI), which is calculated as the weight (kg) divided by height squared (m^2). In clinical terms, a BMI of 25–29 kg/m^2 corresponds to overweight, whereas 30 kg/m^2 plus corresponds to obesity.

Statistical analysis

A commercially available statistical program, Statistical Package of Social Sciences (SPSS 13.0, Chicago, IL, USA) and Medcalc 8.3.1.1.were used. All data is presented as mean and standard deviation (SD). The χ^2 or Fisher tests were used (according to standard application criteria) for univariate qualitative data analyses to assess the differences between the group with LV diastolic dysfunction and the group without LV diastolic dysfunction. Continuous data were analyzed using the t Student test for independent samples or Mann and Whitney U test, according to the normality of data. Multivariate analyses were performed by means of logistic regression. The results were considered statistically significant for a p value < 0.05.

Results

Patients' characteristics

In our study the mean age was 63.6 ± 9.6 years; the group comprised males and females in similar proportions; 51 (35.4%) cases presented with diabetes mellitus, 122 (84.7%) were recorded as having hypertension and 87 (55.5%) patients were smokers. Family history of CHD was present in 36 (25.0%) patients, while obesity was recorded in 74 (51.4%) cases. Prevalence of HF in this series was 45.1% (65 patients, 30 males and 35 females). The group without HF comprised 79 (54.8%) patients (Table 1).

Echocardiographic characteristics

Of the 65 patients with HF, 17 (26.1%) presented with normal diastolic function, 38 (58.5%) had an altered relaxation pattern and ten (15.4%) patients

Table 1. Results of univariate and multivariate analyses of possible risk factors of heart failure after myocardial infarction.

Variables	Univariate analyses			Multivariate analyses	
	Patients without HF (n = 79)	Patients with HF (n = 65)	P	OR (95%CI)	P
Age (years)	63.4 (9.9%)	64.1 (9.2%)	0.651		
Gender (men/women)	42/37	30/35	0.402		
Systolic blood pressure [mm Hg]	145.5 (24.7%)	159.6 (26.2%)	0.001		
Hypertension	62 (68.8%)	60 (92.1%)	0.001	1.8 (0.7–3.1)	0.189
Diabetes mellitus	13 (16.5%)	38 (58.5%)	0.001		
Smoking status	34 (43.0%)	53 (81.5%)	0.001	1.2 (0.7–1.5)	0.246
Family history of CHD	20 (25.3%)	19 (29.2%)	0.913		
Obesity	34 (43.0%)	40 (61.5%)	0.027		
Waist circumference [cm]	98.9 (13.2%)	108.4 (12.3%)	0.001	1.9 (0.8–2.9)	0.134
Body mass index [kg/m^2]	28.1 (6.7%)	32.4 (5.3%)	0.027	1.7 (0.8–2.1)	0.318
Homocysteine [μmol/L]	14.1 (5.2%)	18.9 (10.0%)	0.004	2.05 (1.5–2.5)	0.001
Total cholesterol level [mg/dL]	169.6 (51.2%)	191.4 (45.0%)	0.008	2.1 (0.9–2.4)	0.267
Triglycerides level [mg/dL]	116.1 (57.7%)	147.5 (68.8%)	0.003	2.4 (0.8–3.1)	0.189
HDL-cholesterol level [mg/dL]	44.4 (10.1%)	34.7 (14.7%)	0.001	0.7 (0.3–0.9)	0.035
LDL-cholesterol level [mg/dL]	111.5 (44.6%)	124.4 (40.8%)	0.074		
BNP [ng/L]	143 (49.7%)	382 (37.9%)	0.001	2.3 (0.4–4.2)	0.042
Creatinine [mmol/L]	85 (0.16%)	93 (0.17%)	0.038		

Logistic regression analyses model included: diabetes, hypertension, smoking, body mass index, total cholesterol, triglicerydes, HDL-C, homocysteine, creatinine; HF — heart failure; CHD — coronary heart disease; BNP — brain natriuretic peptide; OR — odds ratio; CI — confidence interval

had a pseudonormal pattern. There were no patients with restrictive pattern in our study group. There were no significant differences between the two groups regarding diastolic function estimated by the transmittal flow velocity variables. LV parameters evaluated by echocardiography in the two groups are shown in Table 2. Regarding the diastolic tissue Doppler parameters, significant differences between the two groups were obtained (Table 2).

Association of homocysteine levels with heart failure

Higher levels of Hcy were found in the study group (Group 1: the low LVEF group, with HF) than in the control (Group 2: without HF). The difference in levels was statistically significant: 18.9 (10.0) *vs* 14.1 (5.2); p = 0.001.

During follow-up, hyperhomocysteinemia > 15 μmol/L was found in 39.9% (26/65) of patients with HF *vs* 27.3% (22/79) of patients without HF (p = 0.01).

The multivariate model included cardiovascular risk factors (diabetes, hypertension, smoking, BMI, TC, TG, HDL-C), Hcy, BNP and creatinine (Table 3) and showed significant predictive values for Hcy (p = 0.001), HDL-C (p = 0.035) and BNP (p = 0.042). The association between elevated Hcy and HF remained significant after adjusting for traditional cardiovascular risk factors (Model 1). Further adjustment for LVEF or LV mass index still returned statistically significant values (Model 2). However, the association between Hcy and HF was no longer significant after adjusting for the presence of diastolic dysfunction estimated by the transmittal flow velocity variables. Despite that, the association between Hcy levels and diastolic impairment evaluated by tissue Doppler still proved to be significant (Model 3). The association between elevated Hcy and HF remained significant after adjusting for creatinine level (Model 4).

Relationship between homocysteine levels and severity of heart failure

Hcy values elevated stepwise with increasing NYHA class (controls: 16.8 ± 5.2 μmol/L, NYHA I: 18.3 ± 4.9 μmol/L, NYHA II: 22.7 ± 6.8 μmol/L, NYHA III+IV: 25.2 ± 5.4 μmol/L and correlation analyses (including patients and controls) revealed a significant relation between Hcy and NYHA class severity of HF (p = 0.001, Fig. 1).

Table 2. Left ventricular (LV) parameters by conventional and tissue Doppler echocardiography of groups.

Parameters	Patients without HF (n = 79)	Patients with HF (n = 65)	P
End-diastolic ventricular septal thickness [cm]	11.9 ± 1.5	12.2 ± 1.8	0.467
End-diastolic LV posterior wall thickness [cm]	12.7 ± 1.3	11.8 ± 2.0	0.332
End-diastolic LV diameter [cm]	48.9 ± 3.7	52.2 ± 4.1	0.186
End-systolic LV diameter [cm]	33.9 ± 2.1	39.4 ± 2.5	0.385
LV ejection fraction (%)	51.4 ± 8.7	38.3 ± 7.6	0.047
LV mass index [g/m^2]	95.7 ± 14.1	99.9 ± 19.2	
Transmitral flow velocity			
Peak E velocity [cm/s]	64.1 ± 12.6	63.4 ± 12.0	0.822
Peak A velocity [cm/s]	61.5 ± 14.7	65.8 ± 17.4	0.285
E-DT [ms]	225.0 ± 23.5	214.9 ± 29.7	0.131
E/A	1.04 ± 0.3	0.96 ± 0.4	0.183
Mitral annular motion velocity			
Peak Sm velocity [cm/s]	8.6 ± 1.3	7.6 ± 1.5	0.621
Peak Em velocity [cm/s]	10.2 ± 3.4	7.1 ± 2.4	0.004
Peak Am velocity [cm/s]	7.8 ± 3.2	9.2 ± 3.7	0.004
E/Em	6.3 ± 3.2	8.9 ± 1.7	0.001

Continuous numerical data were expressed as mean ± SD. Peak E velocity — peak early diastolic velocity of transmitral flow; Peak A velocity — peak atrial systolic velocity of transmitral flow; E-DT — deceleration time from peak to baseline of the early diastolic transmitral flow velocity; E/A — the ratio of E to A; Em — peak early diastolic mitral annular motion velocity; Am — peak atrial systolic mitral annular motion velocity; Sm — peak systolic mitral annular motion velocity; E/Em — the ratio of E to Em; HF — heart failure

Table 3. Risk of heart failure associated with elevated homocysteine.

Model	Odds ratio (95% CI)	P
Unadjusted	2.05 (1.50–2.50)	0.001
Model 1	1.15 (1.09–1.90)	0.034
Model 2	1.02 (1.06–1.93)	0.037
Model 3	1.27 (0.83–1.58)	0.456
Model 4	1.32 (1.02–1.62)	0.041

Model 1 — adjusted for male, smoking, body mass index, history of hypertension, history of diabetes, LDL-cholesterol, and HDL-cholesterol; Model 2 — adjusted for Model 1 variables plus left ventricular mass index, resting left ventricular ejection fraction and left ventricular end-diastolic volume index; Model 3 — adjusted for Model 2 variables plus diastolic dysfunction (defined as impaired relaxation or pseudonormal filling on echocardiography); Model 4 — adjusted for Model 1 variables plus creatinine level; CI — confidence interval

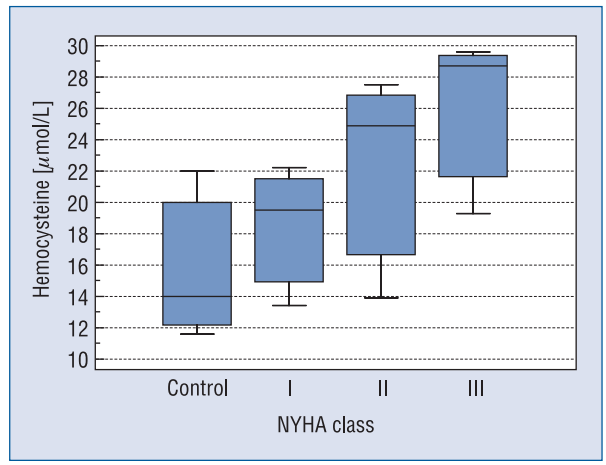

Figure 1. Correlation between homocysteine concentrations and NYHA classification of heart failure.

Analyses also revealed a significant correlation between Hcy levels and HF severity, either assessed by NYHA IV class (p = 0.007), BNP value or quantified by echocardiographic parameters: LVEF (p = 0.023), mitral E/A ratio (p = 0.002) or mitral E/Em ratio (p = 0.043). Univariate results are presented in Table 4.

Discussion

Several recent studies have shown that the elevation of plasma Hcy levels may be an independent risk factor for HF. Hcy seems to induce LVH and cardiac fibrosis which can lead to systolic and diastolic dysfunction, clinically expressed by a significant increase in BNP plasma levels. Our results suggest that the risk for developing HF in patients with previous MI and low LVEF increases with elevated Hcy levels. A significant cross-sectional correlation has been assessed between Hcy and tissue Doppler echocardiography parameters, such as E/Em ratio calculated at the level of the LV lateral wall.

Table 4. Correlation of homocysteine (Hcy) level and severity of heart failure.

	Patients with Hcy < 15 μmol/L	Patients with Hcy > 15 μmol/L	P
NYHA I	8 (27.5%)	5 (13.8%)	
NYHA II	11 (37.9%)	14 (38.8%)	0.007
NYHA III–IV	10 (34.5%)	17 (47.2%)	
LVEF (%)	39.2 (5.9%)	37.3 (5.7%)	0.023
LVMI [g/m^2]	95.5 (13.2%)	102.9 (12.4%)	0.027
Mitral E/A ratio	1.0 (0.3%)	1.5 (0.1%)	0.002
Mitral E/Em ratio	7.8 (1.7%)	9.1 (1.9%)	0.043
BNP [ng/L]	356 (36.1%)	409 (38.4%)	0.031
Creatinine [mmol/L]	87 (0.19%)	98 (0.18%)	0.068

Continuous numerical data were expressed as mean (SD); LVEF — left ventricular ejection fraction; LVMI — left ventricular mass index; Peak E velocity — peak early diastolic velocity of transmitral flow; Peak A velocity — peak atrial systolic velocity of transmitral flow; E/A — the ratio of E to A; E/Em — the ratio of E to Em; BNP — brain natriuretic peptide

Overall, Hcy is an important HF quantification tool, as well as an essential predictor of HF development and evolution.

Some other studies have reported that increased Hcy levels can promote endothelial dysfunction of coronary resistance vessels [18] with increased oxidative stress. Hcy has also been proven to be involved in the induction of cardiac fibrosis, probably by activation of the transforming growth factor-β1 [19] which is known to promote myocardial damage.

Our results confirm the above studies and add new evidence that the inverse correlation between Hcy and LV function is independent of potential confounders among individuals with previous MI.

The positive correlation between Hcy, BNP and HF which we found, has been confirmed by other studies [20]. Previous data has shown that in patients with elevated levels of Hcy, BNP is a sensitive marker which highlights early HF [21], having a high negative predictive value [22]. These studies consider that high levels of Hcy are associated with an increase in the myocardial expression of BNP, with the induction of LV remodeling. Although elevated levels of BNP were not always associated with cardiac remodeling, BNP's antifibrotic and cytoprotective properties have been proved in previous studies [23].

In our study, Hcy levels increased stepwise with increasing NYHA class, revealing a significant correlation between Hcy levels and NYHA class severity of HF. Other studies have shown similar outcomes. One recent investigation showed that an increase in plasma Hcy levels has a stepwise association with the progression of NYHA class (controls: 8.5 μmol/L, NYHA I: 10.3 μmol/L, NYHA II: 12.1 μmol/L, NYHA III: 13.5 μmol/L, NYHA IV: 17.4 μmol/L) [24].

The present study reports the cross-sectional correlation of plasma Hcy with echocardiographic LV parameters. Our data shows that LVEF values were inversely correlated with Hcy levels. However, a statistically significant correlation between Hcy and commonly used markers of HF, such as LVEF and NYHA class, was not established [25]. We found a strong correlation between plasma Hcy and LV diastolic dysfunction, similar to the results of the Framingham Heart Study [5].

The Physicians' Health Study showed that a moderate increase in plasma Hcy levels trebled the relative risk for mortality from cardiovascular disease and MI [26]. However, after further follow-up, this association proved not to be statistically significant [27]. Elevated Hcy levels were independently associated with the incidence of stroke, as well as with cardiovascular disease and all-cause mortality in the Framingham Heart Study [28]. However, such positive associations were not reported in all studies. Folsom et al. [29] have demonstrated in the ARIC study that adjustment for other CHD risk factors cancelled the association of incident CHD events with Hcy.

The prospective Caperhilly Study [30] differs from our results, as it excludes high levels of Hcy as a potential risk factor for acute coronary events in a CHD-free middle-aged male population. Few prospective epidemiological studies on subjects initially without CHD have shown similar findings. A recent meta-analysis indicated that in healthy subjects, Hcy levels are only weakly related to cardiovascular disease risk [31]. More recently, evidence for an association between Hcy and the prevalence, as well as the incidence, of HF has been postulated. Among patients with HF, elevated plasma Hcy levels have been previously reported [20, 25]. Moreover, in a prospective study of 2,491 adults, Vasan

et al. [4] demonstrated that the risk of HF during an eight year follow-up was positively associated with baseline Hcy concentration.

Our research did not show any significant correlation between Hcy concentration in patients with elevated plasma creatinine levels and the incidence of HF. In other studies [32], Hcy levels in chronic kidney disease patients were assessed and the incidence of cardiovascular events was evaluated. Plasma Hcy was not significantly correlated with cardiovascular morbidity and mortality in patients with moderate renal impairment. The effect of Hcy on cardiovascular disease was not significant when adjusted strictly to glomerular filtration rate.

Limitations of the study

We admit that the data from our study should be validated by other reports. The first limitation is the cross-sectional design itself, with case ascertainment and time elapsed between the myocardial event and the moment of study as possible bias sources. Secondly, in some subsets, because of the limited number of patients, we were unable to properly demonstrate a real correlation between Hcy and HF. Further research is needed in order to establish a clinical protocol regarding the use of Hcy levels in patients with HF.

Conclusions

Increased plasma Hcy levels independently correlate with the severity of HF in patients with chronic MI. We suggest that Hcy can be used in clinical practice as a valuable HF risk marker in patients with chronic MI. However, present data is insufficient for developing a clinical protocol. The cost of Hcy dosage prohibits its use at present, but if the prognostic value of Hcy levels is confirmed by larger studies, such an assessment could become cost-effective.

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